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Time to chart Europe's future

Britain is once more the black sheep of Europe, after another row about agricultural policy, but the event is also an opportunity. Somebody should seize it.

This is turning out to be a bad year for the European Community. After what should have been a cheerful twenty-fifth anniversary (see *Nature* 25 March, p.278) that had most member governments asking "What have we done wrong?", a quarrel redolent of the turbulent 1960s has broken out between Britain (assisted by Denmark and Greece) and the six other states. The issue is that which has dogged the Community since it began — the price to be fixed for agricultural products in the year already under way. British unwillingness to agree to price increases exceeding 10 per cent had been well advertised in advance, as had the British government's insistence that this year, as in the past two, it should pay less towards the common budget than the rules of the Community require. With other things on its mind (see below), the British government obviously failed to sense that if it stuck to its position, the convention that any member state can veto any proposal would not save it from being voted down. This, in the event, is what happened. In the next few weeks, the member states will be looking for some way of picking up the pieces.

That will not be easy. Ever since it joined the European Community in 1972, the British government has been grumbling about the common agricultural policy, in effect a device for paying European farmers well so as to produce more food than Europe can consume. For much of that time, the British have been chipping away at the policy, and not always in the most high-minded spirit. Only a few weeks ago, a British agriculture minister was boasting to the House of Commons how he and his colleagues had managed to dip British hands into the pork barrel, winning more than a quarter of a new subsidy on suckling cows and virtually the whole of the novel subsidy for sheep. The difficulty, which successive British governments have been slow to recognize, is that the common agricultural policy, the constant but of their complaints against the Community, is as much a political necessity for other member states as is the right to veto any proposal judged to touch a vital issue is for Britain. These are eminently circumstances that call for compromise and self-restraint. Pretending that the truth is otherwise will lead nowhere. The ideal is that the common agricultural policy should wither, perhaps because it is overtaken by farmers' recognition that, in the modern industrial state that Europe seeks to be, there are more interesting and profitable things to do than till the land. What the Community should be looking for, in the rowdy weeks that lie ahead, is some means of making that ambition come nearer.

The difficulties are nicely illustrated by the grand French plan to do something within the Community about the commercial challenge from Japan in the electronics industry (see page 257). The obvious objection to the French plan for the revivification of the French electronics industry is that it is a national plan, and one based on the substantial investment of government funds. Even if the enthusiasts for the scheme were able to recruit the funds they seek, and if their use of them were wise, the result would merely be to make the electronics industry in the rest of Europe even more hard-pressed than at present. The result of that would be to renew the clamour that national governments should do even more than at present to help their own domestic manufacturers, perhaps by putting more business their way. The end result would be a system not very different from that now embodied in the common agricultural policy — a European electronics industry protected

from the outside world by high tariff barriers, selling its products at prices that are too high and competing fiercely with itself. That is not a recipe for meeting the challenge from outside but, rather, a recipe for continued failure. The government of France seems not to appreciate that the Japanese success in electronics has been founded on an accurate appraisal of the international market, and that the only effective counter — admittedly only a first step — is to make the European market in electronic products thoroughly international. So will the French, and their Community partners, give up their present policies of channelling public contracts towards their domestic companies? Not, the guess is, without a struggle.

That, however, is precisely the struggle on which the British government, blackballed last week in Brussels, should now embark. The fact that the electronics industry in Europe is closely linked with defence, specifically exempted by the Treaty of Rome from the rigours of the open market, is not the stumbling block it seems but rather the opposite. It is foolish that half of the ten governments in the European Community should be spending large sums of money on the solution of essentially similar problems, hoping to recover part of the cost by sales of advanced military equipment overseas. Why should not each of them spend less on research and development, selling the products to each other in the first place? The result could well be that member states' strategic independence would be compromised, but is it seriously suggested that the constant rows within the European Community imply that one day it may be necessary for the members to attack each other? The pretence of military independence in which the member governments of the European Community at present luxuriate is belied by what their electors know — that culturally the Community is already so much of a piece that unscrambling it would be literally unfeasible. The advantage to the British government of taking the initiative on this issue of electronics and, where necessary, defence, is that it could throw those who baited it last week onto the defensive, yet hope to emerge with a prize to offer its own people that would be at least as valuable as the cost of the agricultural policy.

Rules for limited war

The Falkland Islands conflict marks a step towards the automation of conventional war.

The politics of the Falkland Islands war is outside *Nature's* bailiwick, but the technology is not. For what is happening now in the South Atlantic is probably a foretaste of what may happen all too often in decades to come. First, it is a limited war in which neither side seeks the comprehensive capitulation of its adversary. Second, it is a high-technology war in which the combatants are equipped with virtually automatic weapons developed against the possibility of conventional conflict in Europe, but now being used in a mercifully remote part of the world, one so distant that other states are unlikely to be drawn in. What lessons, spine-chilling and otherwise, can be drawn from what is now going on?

That limited wars, out of fashion since the eighteenth century, are still feasible should not be a surprise. The Yom Kippur war of 1973 was limited in the sense that the Israeli objective was the capture of a tract of territory, the Sinai desert up to the Suez



Canal, and not the destruction of Cairo or of the Egyptian state. This self-imposed restraint was not based on high-minded principle but on a calculation of what might be accomplished without dangerously broadening the conflict, reinforced towards the end by the discovery that Egypt was well-equipped with surface-to-air missiles. (We are all lucky that the calculation was not disproved.) Similarly, the involvement of the United States in the long war in Vietnam was limited; it was tacitly understood that nuclear weapons could not be used without triggering off a broader conflict that the United States did not seek. The same is true in the Falkland Islands. The United Kingdom has a modest stock of nuclear weapons, some conveniently carried on submarines, but their use is unthinkable and has not been mentioned. Even the wild talk in Britain that it might be necessary to attack airfields in Argentina has quietened as the sober realities of conflict have dawned, and as the importance of public and political opinion elsewhere in South America has been appreciated.

What this implies is that limited wars are possible only with the tacit agreement, however grudging, of other interested parties. And because other states' opinions can change, the combatants must spend a substantial part of their energy persuading everybody who is prepared to listen that they are acting reasonably, or at least as reasonably as is consistent with their resort to violence. This, no doubt, explains why the Falklands conflict has so far been conducted with extraordinary civility. The substantial British community in Argentina has not been unduly harassed, while in both capitals journalists go normally about their business (although three British journalists have been wrongly locked up in Argentina for six weeks, and three others kidnapped for a day). In Britain, the only untoward incident has been the decision last weekend by the Tottenham Hotspur football club that its talented Argentine player should be dropped from Saturday's cup final. Both sides have an interest in continuing like this, for to behave otherwise would weaken the cases they are putting to their friends.

Against this background, the British government has made two important errors. First, it has unnecessarily sought to keep to itself news of what is actually happening in the Falkland Islands. Second, no member of the British government has yet made the conciliatory speech that circumstances demand, making the simple point that the traditional links between Britain and Argentina need not be jeopardized by what is going on and even that the present Argentine government, while not democratically elected, is less fiercely repressive than its predecessor. Indeed, it would be entirely consistent with the notion that the Falklands war is strictly limited that even now the British government should be prepared to negotiate the kind of settlement it will be prepared ultimately to countenance. For the time being, both sides are stuck on the abstract concept of sovereignty; sooner or later, they will have to settle among themselves some kind of monetary price at which that concept could be made more flexible (see *Nature* 8 April, p. 480). One of the tricks in fighting a limited war is to help opponents to give up the struggle at the earliest opportunity.

Technologically the Falklands war is far from limited. Reports that troops under air attack are unnerved not to see the attacking aircraft but only the missiles sent automatically to bring them down are vivid and credible, but that is what conventional warfare has become — a technicians' war. The past few weeks have shown that vehicles carrying people, whether ships or aircraft, moving in an environment in which radar detection at long range is technically straightforward, have become exceedingly vulnerable to attack. As missile ranges lengthen, they will become more so — which should give pause to the now-vociferous British naval lobby. Long-range attacks on ground targets are for the time being more difficult and still require human intervention, but the development of conventional battlefield weapons in the past decade suggests that even that relative immunity will not persist indefinitely. It does not, of course, follow that people will cease to matter. On the contrary, their roles as gatherers of intelligence and as communications links between pieces of equipment will become more important while their numbers shrink and as their

skills increase. This inexorable trend points to several circumstances. First, limited war becomes more feasible as the chances of large numbers of military personnel being killed diminish. Second, the cost of military preparations is bound to increase. Third, there is a limit to the extent to which the depersonalization of conventional warfare can be carried without the combatants deciding that they must force a decision by using civilians as hostages of a kind. None of these prospects is cheerful.

Rothschild rides again

Lord Rothschild's report on social science research is predictably intelligent and subversive.

Once upon a time, the story goes, there was a wicked fairy called Sir Keith Joseph, Secretary of State at the Department of Education and Science in the United Kingdom. One day last year, soon after his appointment (some say demotion) to that office, Sir Keith took the daring step — it was at least unprecedented — of cutting half a million pounds from the recommended budget of an innocent but youthful mainstay of British academic life, called the Social Science Research Council or SSRC for short. Anxious to dissemble the extent of his wickedness, Sir Keith said that he would leave it to Lord Rothschild, a scientist and merchant banker who acquired in 1971 a fearsome reputation for angering academics, to recommend whether or not this stripling outfit should continue to exist. Thanks to the journal *New Society*, it soon became known that Sir Keith had been dutifully promising the Chancellor of the Exchequer (by definition wicked) that *something* would be done about SSRC. Thunder and lightning occurred.

Wicked fairies have no luck. How could Sir Keith have known that his chosen companion in malevolence had earned his reputation for wickedness by his flair for telling the truth and doing it deftly? Lord Rothschild's report on the issue last week (*An Enquiry into the Social Science Research Council*, Cmnd 8554, HMSO, £6.50) is in that tradition. For as nice a statement of the case for social science, and a neat dig at Sir Keith in the process, what could better the fifth paragraph of his report?

Einstein is reported to have said that "Common sense is a deposit of prejudice laid down in the mind before the age of eighteen". Yet to the layman — the man in the street — many of the problems on which social scientists work are either too far fetched or do not need further work because common sense answers are already available. Common sense tells us that:

- (1) Capital punishment deters potential murderers;
- (2) The import of foreign cars should be drastically curtailed;
- (3) There should be more small hospitals and fewer large ones;
- (4) Horror comics make children violent (USA).

Are we sure that common sense is right? Might there not be a layer of prejudice or even ignorance?

So, this is how the story goes, Lord Rothschild turns out not to be a wicked fairy's hatchet-man, but a good fairy in disguise. The youthful SSRC has been misjudged, he says. Too many have expected too much of it too soon, and without a proper understanding of what academic life or the social sciences are like. So the SSRC should be reprieved, first from the burden of being "looked at" for at least the next three years. In gratitude, however, it should be prepared to move to Swindon, should be more (not less) courageous and should defend itself against the single open charge of left-wing bias. Wicked fairies everywhere will be discomfited by this sane and unchallengeable opinion. One of these will be the British Academy, which calls itself "the national learned society representing the interests of the social sciences", and which took the lead in bad-mouthing the SSRC a year ago. Lord Rothschild (who is evidently not unalloyed good fairy) quotes a pompous passage from the academy's written evidence saying (truthfully) that it is incompetent to be the SSRC but promising that it will be "vigilant" in overseeing the council's work. Can everybody live happily after that?

UK plutonium worries US Senate

Alarm at link between civil and bomb uses

Washington

US senators may soon start investigating the fate of as much as four tons of fuel-grade plutonium that the United Kingdom supplied to the United States over several years on the understanding that it would be used only for civilian purposes, but which may have been put into nuclear warheads by US authorities. The plutonium originated in the Magnox reactors of the Central Electricity Generating Board.

Last October the two governments apparently agreed that the United Kingdom would resume providing plutonium to the US Department of Energy (DoE) to help indirectly with the DoE's programme for producing and modernizing US nuclear warheads.

Under a previous barter agreement that ran from 1964 to 1971, the United States supplied the United Kingdom with highly enriched uranium for its nuclear submarine programme and with tritium for UK nuclear weapons. In return, the United Kingdom supplied an unspecified amount of plutonium from Magnox reactors. The terms of the accord have always been secret, but in 1964 a British government spokesman indicated that the United States had no intention of using the plutonium thus obtained for nuclear weapons. Now, however, Senators Gary W. Hart (Democrat, Colorado), Alan K. Simpson (Republican, Wyoming) and George J. Mitchell (Democrat, Maine) seem likely to act on a request from a public interest group that they look into how much plutonium was shipped to the United States between 1964 and 1971.

The Senate investigation reflects a growing concern in the United States about DoE's plans to link civilian and military nuclear programmes, a move away from the historic separation between "atoms for peace" and "atoms for war". Recently, DoE has announced that there is a "shortage" of plutonium (DoE designs and builds nuclear weapons for the Department of Defense). So it plans to take plutonium from spent fuel from several civil research reactors to fashion more weapons grade material.

DoE also wants to convert the 17.8 tonne stockpile of fuel-grade plutonium now destined for the breeder reactor at Clinch River, Tennessee, for weapons use. This stockpile may well include much or all of the plutonium supplied under the barter agreement. "Either it is in the US nuclear weapons already, or it is in the stockpile

meant to fuel the breeder, but now destined for weapons," says S. Jacob Scherr, senior staff attorney for the Natural Resources Defense Council Inc.

According to the Natural Resources Defense Council, existing US nuclear weapons utilize about 90 tonnes of plutonium (plus or minus 15 tonnes). Current weapons-grade plutonium production by DoE has run about 1.4 tonnes per year, but DoE wants to step this up to 2 to 3.5 tonnes annually. In October, the UK government allegedly agreed to send more plutonium to the United States. The British plutonium may be going to fuel the breeder at Clinch River so that fuel otherwise destined for the breeder can be diverted into nuclear weapons. John Moore, Parliamentary Under-Secretary of State at the UK Department of Energy, was questioned about the plan in March.

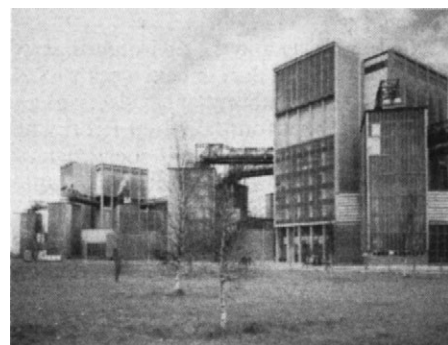
DoE seems likely to continue to press the United Kingdom for more plutonium, because Senators Hart, Simpson and Mitchell have succeeded in cutting off another possible source — by a vote of 88 to 9, on 30 March, the Senate voted for an amendment to prohibit DoE from using spent fuel from commercial reactors for its nuclear weapons programme. In a debate in the House of Commons on 21 December 1981, Mr Moore emphasized that civil plutonium sold to the United States would be subject to international safeguards, but he implied that military plutonium transferred under the defence agreement would not be so restricted.

Oak Ridge up for grabs

Washington

On 3 May, the Union Carbide Corporation, which has run government atomic facilities at Oak Ridge, Tennessee, since the Second World War, announced that it no longer wants to do so. Union Carbide is not seeking to renew its option to manage Oak Ridge when the present contract expires on 30 September 1983. Recognizing the dislocation that its decision could cause, however, the company says it will stay on for up to three years longer if necessary.

The names Oak Ridge and Union Carbide have been almost synonymous in government science circles and in the Tennessee Valley region since the first gaseous diffusion plant was built there, amid great secrecy, during the Second World War. At that time, the company was heavily involved in manufacturing carbon products, but has since grown (its 1981 sales were \$10,000 million) and diversified into batteries, antifreeze, car care products, even salmon farming and ferroalloys. But earnings have been down of late, and the company has been divesting itself of activities which are not central to



The Magnox at Berkeley in Gloucestershire — source for US bombs?

DoE has also decided to proceed with the Laser Isotope Separation facility at Lawrence Livermore Laboratory, which would cost an estimated \$560 million and which the Natural Resources Defense Council claims has no justification other than to enrich plutonium from civil reactors to weapons-grade material. DoE also seeks to build a decladding plant to utilize fuel from noncommercial plants, such as the Fast Flux Test Facility at Hanford, Washington.

The issue at stake is not only the historic separation between civilian and military nuclear programmes, but also the precedent that DoE is setting for other countries. Critics of DoE's plans argue that if the United States starts taking civilian spent fuel from its weapons programme, it will not have a leg to stand on when it tries to dissuade other countries from doing likewise.

Deborah Shapley

its purpose. So it is shedding Oak Ridge.

Union Carbide is one of the most respected corporate managers of any government laboratory in the nation. It actually runs four facilities — Oak Ridge National Laboratory, the Oak Ridge gaseous diffusion plant, the Oak Ridge Y-12 plant that makes nuclear weapons components, and the gaseous diffusion plant in Paducah, Kentucky. Union Carbide's act will be hard to follow.

The government spends about \$1,000 million a year on these facilities, paid through the company, which has 18,000 employees working there on its payroll. Its fee for the operation is \$8 million per year, from which come some expenses. The Department of Energy, which holds the contract with Union Carbide, may decide to open four separate bids, one for each of the facilities, rather than ask a single company to follow in Union Carbide's footsteps. As a side effect, this might hasten changes in the mission and role of the Oak Ridge laboratory itself, which is under White House review, along with the other departmental laboratories.

Deborah Shapley

Hamburg elections

Power politics

Heidelberg

Nuclear power and the environmentalists will play a crucial part in next week's local elections in Hamburg. The election on 6 June will be a four-cornered fight. The looseness of the traditional social democratic grip on the Hanseatic city state reflects the party's national difficulties. Mayor Klaus von Dohnanyi may well be returned, but with a minority in the senate. Proposals for a *gross Koalition* between the Christian Democratic Union (CDU), the second largest party, and SPD have been dropped. The Free Democrats (FDP), aligned to SPD, are fighting for the 5 per cent vote needed for survival under the proportional representation rules. But the crucial minority, likely to get 8–10 per cent of the vote, is the Grün-Alternative Liste (GAL), an umbrella party of some 150 groups based on issues ranging from citizens' protection and women's rights to environmentalism and opposition to nuclear power.

Mayor Dohnanyi would apparently be willing to attempt a minority administration with GAL cooperation. Despite the difficulties of arriving at even an internal GAL consensus, and despite its preference for a role in opposition, GAL may agree. But its terms include rejection of the new *Energiekonzept*, the controversial product of long hard bargaining between Hamburg and the Hamburgischen Electricitätswerke (HEW).

These plans, announced on 27 April and heralded as classic reforms, involve going ahead with what is probably the country's most disputed nuclear reactor, at Brokdorf, and also the construction of four conventional coal-fired power stations with heat-coupling. Under the previous plan, 70 per cent of Hamburg's electricity was to have come from nuclear reactors; this has now been reduced to 25 per cent with the possibility of extra conventional capacity that would allow Brokdorf to be abandoned by the year 2000. HEW will invest DM3,000 million for the electricity-heat project and DM2,500 million for Brokdorf. DM50 million will be contributed by the federal government, which sees the plan as a pilot project for integrated energy supplies in built-up areas. A third of a million homes will be heated, 1,500 jobs created, 140,000 tonnes of oil saved, and pollutant emissions significantly reduced.

The plan provides ammunition all round. GAL insists on withdrawal from nuclear power plants at Brokdorf, Brunsbüttel and Krümmel. Nor is the prospective advent of a friendly neighbourhood coal-fired power station, however smart, pleasing to that diverse conglomeration. Within SPD, nuclear power is strongly supported by the federal government but

rejected by both Social and Free Democratic Parties in the north. The local Hamburg SPD voted last year for withdrawal from Brokdorf and the previous mayor, Hans-Ulrich Klose, resigned on the issue. The new plans split Dohnanyi's home base and may well drive SPD left, nearer to the "Greens".

Despite Dohnanyi's sleight of hand, his attempt to back the nuclear power issue both ways may leave him stranded. The Christian Democratic mayoral candidate, Walther Leisler Kiep, has attacked the financial basis of the project and the move from clean environmentally favourable nuclear energy to coal, predicting higher energy prices and an electricity gap if local objections slow construction of the coal-fired power plants.

Peter Glotz, party executive secretary, compares the social democratic response to the unwieldy manoeuvres of a tanker. If Hamburg's "Greens" reach the bridge, the Dohnanyi *Energiepolitik* may go overboard and the national supertanker be on course for a dry dock.

Sarah Tooze

East-West energy trade

Pipeline ploy

President Reagan's visit to Europe next month will include major talks on the future of East-West trade. The immediate issue is that of the interest rates to be demanded of the Soviet Union. The Americans' wish to increase them is opposed by some West European countries, notably West Germany, which feel that if the Soviet Union is reassessed, several other countries should be treated likewise.

The Soviet Union has a chronic shortage of hard currency. One possible means of repaying loans would be a counter-trade in fuel, particularly natural gas, which during the 1980s will increasingly replace oil as the Soviet Union's major fuel export. French and West German contracts for deliveries of gas from the Urengoi field originally caused the Americans considerable concern. Of late, however, they appear to have accepted European arguments that the amounts involved (10,500 million cubic metres for West Germany plus 700 million for West Berlin and 8,000 million for France) form only a small proportion of the energy budget, and do not constitute dependence. However, the signing of a contract last week for the supply to Switzerland of 360 million cubic metres of gas annually for 30 years suggests that other West European customers for Soviet gas might not follow the comparatively small demands of France and West Germany.

The transfer of technology, heavy-duty pipelines and compressor equipment, as part of the initial Western investment in the pipeline, continues to worry the Americans, although little or nothing is involved that had not been made available to the Soviet Union ten years ago.

A recent survey of East-West energy trade, however, suggests that the lack of a coherent Western policy could considerably weaken the position of the NATO countries in the changing energy situation of the 1980s. The survey's author, Jonathan Stern, describes a dual energy scenario for the 1980s.

On the one hand, Stern says, an endemic energy shortage will develop in Eastern Europe which will only be made good by purchases on the hard-currency market. Under present agreements, the Soviet Union cushions increases in the price of oil and gas to the Comecon countries, but only up to an agreed amount, leaving an increasing gap to be filled from the world market. Unless the Comecon countries can agree with the oil producers to purchase oil and gas with soft currency, foreign debts

"WE'VE COME TO READ
YOUR METER."



will escalate and political and economic tensions will increase.

On the other hand, gas exports are an attractive hard-currency earner to the Soviet Union. Construction of the pipeline, in spite of the delays imposed by the US sanctions after the military takeover in Poland, is likely to go ahead, and once the pipeline is in operation, further contracts with the West are likely.

A coherent Western policy, Mr Stern urges, should therefore be worked out, based on the following criteria:

- Are other gas suppliers a more acceptable security risk?
- Are the security risks outweighed by related contracts?
- What would the Soviet Union achieve by cutting supplies (granted that it would lose more than 50 per cent of its hard currency earnings by doing so)?

Lack of such a policy, Mr Stern argues, would not only allow the Soviet Union to claim a political victory (by pointing out cracks in the Western alliance), but would also weaken the Western bargaining position in dealing with the other aspect of the East European energy problem — the efforts of the energy-poor countries of Eastern Europe to top up supplies on the world market.

Vera Rich

Information technology

Send more bits

The age of electronic mail is about to dawn in Europe, not traditionally the leader in new information and communications technologies. Before the year is out, most European telecommunications administrations are expected to introduce a new international standard that will allow word processors to communicate with each other through existing telephone and data transmission networks.

With its penchant for confusing names, the information technology community is calling the new service "teletex". It is, however, a far cry from teletext, the broadcast information service. Teletex is either a sophisticated form of telex or a standard that allows computer terminals to communicate with each other.

The teletex standard was adopted by CCITT, the international telecommunications standards agency, at the end of last year. Europe's enthusiasm for it stems from the present difficulty of linking incompatible word processors over telecommunications links. The United States, which might be expected to be the largest market, is reluctant to adopt the standard, chiefly because the already-large word processor market makes it worthwhile for manufacturers to adopt their own communications standards.

Theoretically, it should be possible to write teletex-compatible communications software for any type of word processor. The practical difficulties, however, have persuaded manufacturers to design specific teletex machines. Among the leaders are Siemens of West Germany, which already produces teletex equipment compatible with the German data network. Other companies, either selling teletex machines in some countries or promising them soon, include Philips, ITT Creed and IBM.

Teletex's chief attraction is that, in many instances, it can deliver documents much faster and more cheaply than the ordinary telex or the post. As it is basically a word processor, it can also relay information in different formats, unlike telex. Most telecommunications administrations will be introducing services with transmission rates of 1.2 kbits per second, doubling this later on. Using the lower data rate, a typical A4 page of text (*Nature's* page size) will take roughly 30 seconds to transmit.

The cost of using the service will depend on the charging policy of the different telecommunications administrations. British Telecom, for example, will be making a "small" service charge but will thereafter charge for time at the ordinary tariff. At current rates, one A4 page would cost 12.9 pence to send a distance of more than 56 kilometres between 8 a.m. and 1 p.m. over the public telephone network. Forty-three A4 pages, however, could be sent within the same city after 6 p.m. for only 4.3 pence. These charges should be

compared with the cost of a first class stamp, now 15.5 pence.

The capital cost of equipment is still uncertain, but manufacturers expect teletex machines to cost no more than sophisticated word processors.

The service to be launched throughout Europe this year will be relatively simple, but a facsimile standard is expected later. British Telecom's service will initially be suitable only for communicating between teletex machines through either the public telephone or packet-switched data networks. However, the service is expected to expand in 1983 to allow communications from teletex to telex machines.

West Germany, which introduced its own teletex standard in part compatible with the international standard, has already launched a service. Manufacturers that have supplied to the West German market, however, may not be able to sell their equipment in other countries without first modifying it for other networks.

US companies showing an interest in teletex seem to be those with a strong interest in Europe. IBM is planning a teletex version of its display writer word processor and Western Union is also apparently developing teletex. Canada, however, is not showing its neighbour's reluctance. It also plans to introduce a service this year.

Judy Redfearn

French electronics

Rushing ahead

Has the French electronics plan come too late? M. Abel Farnoux and his team at the Ministry of Research and Technology in Paris have laboured for eight months to produce a grand plan for the whole French electronics industry, from primary materials right through to consumer products and computer components. Its coherence and grandeur are marvellous to behold, but news is still awaited from the Council of Ministers about the scale on which it will be financed. Twelve months ago the new government was full of expensive plans; more recently, the finance minister reckoned up the bill.

Nevertheless, Farnoux and his chief — science minister Jean-Pierre Chevènement — are pushing the plan strongly. The plan must be implemented "within a year" to be effective, they say.

Alongside industrial expansion, it would increase research and development in electronics and related fields by two-thirds, relative to the 1980 figure of FF 12,000 million, to FF 20,000 million in 1986. The strategy would cover the whole industry and not just the present strong points of telecommunications and telematics, and it would be aimed at bringing France closer to the levels of the United States and Japan. (Electronics for the French defence industry, third in the world's armaments league after the United States and Soviet Union, is also included in the strategy but

has been omitted from published versions for security reasons.)

Nevertheless the published report says that electronics is a "basic technology at the heart of our defence and communications systems". Strength in electronics would also permit "indispensable gains in productivity" in other industries; open up vast consumer markets; contribute to energy conservation in new energy technologies; directly and indirectly reduce the French trade deficit; and (a point added for Mitterrand?) play a major role in "cultural" affairs.

The industry (or *filière*, as the French call a collection of industries taking a raw material to a product) must be treated as a whole, says Farnoux; for him it is all or

Division of the world electronics market, according to the recent French report

Country	Production (\$10 ⁹)	% Of world production	Trade balance (\$10 ⁹)
USA	134	46	+4
Japan	46	16	+13
West Europe	76	26	-6
(Germany)	23	8	0
(France)	17	6	-0.2
(UK)	15	5	-0.2
Others	35	12	-11

nothing. Japan and the United States must be met head-on: it is no answer to manufacture American and Japanese products under licence, says the report. European cooperation should be sought, particularly in the development of new micro-electronic consumer products.

In France at least, a big training programme will be necessary: up to 1990 the report envisages the creation of 75,000 "engineer-researchers", 25,000 senior technicians and 400,000 skilled workers.

If the report were adopted in full, there would be 14 national projects, including a large French scientific and industrial computer, chip manufacture, electronic publishing, computer translation and others. M. Chevènement has announced the setting up of working parties on each project, independently of the report's adoption by the Council of Ministers.

On research, new units would be set up combining both academic and industrial interests. Government investment in research would rise (50 per cent of the French electronics industry is now nationalized, with 30 per cent in American hands and the rest in private French ownership) but mechanisms would have to be found to give a better return on each franc. The weak areas in current research are seen to be information and communication science, solid-state physics and chemistry. Mathematics and robotics are considered well advanced.

One final recommendation may not be well received by M. Chevènement, however. After a long exercise in gathering the instruments of technology politics under one roof, the minister is now faced by a proposal to create a secretary of state for electronics.

Robert Walgate

Science in US Congress

Fair winds

Washington

The apparently pro-science and technology mood of Congress this session, particularly in matters involving private industry, is indicated in much of the routine business of bills introduced, of bills reported out of subcommittee (which means that a small number of congressmen agree something should be done), of bills reported out of full committees (which means that a larger group of congressmen agrees), and by bills actually voted by either the House or the Senate.

True, Congress is not rushing through sweeping reforms. Indeed, it is unlikely to do much — in terms of legislation passed by both houses that then becomes law — that will change the face of US science. The Republican party dominates the Senate; Democrats have a majority in the House. Democrats are preoccupied with the budget battle, while the Republicans tend to be thinking of the next election.

One measure with a chance of passing is a patent reform bill (the Uniform Science and Technology Research and Development Utilization Act or S. 1657 in the Senate). This would extend to most organizations performing government research the patent reforms enacted last year for small businesses, non-profit institutions and universities. It would also unify the patent policies of the various government agencies. The long-standing question has been when a researcher using government funds is entitled to hold the patents arising from the work, or when patent rights should go to the government department that sponsored the work. The present congressional mood includes greater consensus that federal shackles be removed, allowing researchers the greatest incentive to market their products.

Another bill, the Joint Research and Development Act (HR. 6262 in the House), is a response to the US high-technology industry's complaint that other countries allow industries to pool talent on research problems but that, in the United States, such pooling risks violating antitrust laws. The bill would allow the government's lawyers to issue a certificate permitting joint research and development in selected cases, and protecting the companies from antitrust prosecution.

The Senate has passed the Patent Term Restoration Act (S.255) whose counterpart is now in the House Judiciary Committee, but may not emerge before Congress adjourns in September. It tries to help industries that the government regulates to recoup more money from patents, to compensate for the costs of regulation. At present pharmaceutical companies file for a patent as soon as a new compound is discovered. The patent runs for 17 years, of which several are used to develop the compound into a marketable drug. Then

the firm must file for permission to market from the Food and Drug Administration. By the time the drug is approved for marketing, which can take up to 10 years, the company has only a few years left in which to recoup its investment. The pharmaceutical industry claims that this delay can cost \$70 million for a single drug. The new bill would extend the lifetimes of certain patents by up to 7 years.

In the Senate especially, legislators seem concerned with freeing industry and assisting US high-technology trade. A resolution has been introduced to guide the imminent talks in Geneva concerning the General Agreement on Tariffs and Trade (GATT), that refers specifically to US high-technology trade needs. Another bill, passed by the Senate, would fund a special clearing-house to help move the government's enormous store of technical information into the private sector. A further measure introduced in both houses would offer tax credits to manufacturers of computing equipment which give hardware to schools. The measure was promoted by one of the founders of the US home computer company, Apple Computers.

If sentiment were more like that of ten years ago, when faith in federal government intervention was far stronger, Congress might now be designing large federal programmes to "rescue" the US high-technology industry, or greatly increasing spending on federal research and development. Instead, there is a feeling that government is not very good at picking winners and that the congressmen want to encourage promotion of technology in the marketplace. This attitude, particularly prominent among Republican senators, is in contrast to past enthusiasm for heavy federal involvement and big government development and demonstration programmes. Basic research has benefitted from the change — both those who favour more federal intervention and those wanting to promote technology in the marketplace view basic research as an essential government investment.

Likewise, the cause of improving US science education in the schools has support from both sides. Senator John Glenn (Democrat), the former astronaut who has made science and technology a main plank of his political activities, has introduced a bill (S.2421) to set up a council in the National Science Foundation to suggest a cure for the "technological illiteracy" of the nation. It would be given \$5 million to come up with the plan, and \$50 million per year for four years to implement it. A similar bill has been introduced in the House by Don Fuqua (Democrat) and Doug Walgren (Republican). Neither bill is likely to get very far. But the momentum these congressmen are giving to the issue of science education may promote a change of heart from the Reagan Administration, until now opposed to a major federal role in science education. **Deborah Shapley**

Computers for free

The US computer industry is joining the ranks of those crying for improvements in education in science and engineering offered in US schools and colleges. As a result, the National Science Foundation (NSF) is expected to announce in early June that five computer companies will be donating many hundreds of individual computers to help solve the growing problem of "technological illiteracy".

It all began when two computer companies — as yet unnamed — each tried to donate 100 machines to NSF for distribution to schools. This gift, however, set NSF bureaucrats worrying whether it was legal to accept this largesse. As it turned out, NSF, unlike some other government agencies, has specific statutory authority to accept gifts that are for the purpose of furthering NSF's missions.

But NSF did not want to be seen to favour these two computer companies over any rivals for the honour of giving away their machines to the government. So they went through a moneyless bidding process, and invited gifts from all companies. Now, NSF sources say, five companies will be making the donations, although the terms, the nature of the hardware, and the institutions they will be given to have not yet been revealed.

Why is the computer industry so eager to provide free samples to young people in the schools and colleges? One answer, of course, is that a student who learns an elementary computer tongue at school will outgrow it and ask for another model. Company sales would not be hurt. **Deborah Shapley**

British universities

More misery

Hopes that the British university system would be spared some of the government's economy measures were dashed last week, when the University Grants Committee made public the recurrent grants to individual universities for the academic year 1982-83. There is no substantial change from the provisional allocations of a year ago, although the University of Salford, one of the most seriously afflicted then, has been given an extra year in which to reduce its establishment.

The coming academic year will be the second of the three in which government subvention for the universities is to be reduced by 8.5 per cent. The sum now offered to the universities is, however, larger than the amount advertised last year because allowance has been made for inflation (4 per cent on salaries, 9 per cent on other costs) and because the University Grants Committee has been given more

than £100 million extra to compensate universities for the reduction of fees for home students.

For many British universities and academics, last week's announcement will seem to bear directly on the pay negotiations now under way between the universities and university teachers, represented by the Association of University Teachers. For the grants committee's letter does formally confirm the UK government's intention that the university grant for the coming year should include only 3 per cent for salary increases. While there have been some suggestions, at the University of Aberdeen for example, that academics might forgo pay increases in the present round of pay negotiations, the union nationally is asking for 14 per cent, 12 per cent to compensate for price inflation in the past year and 2 per cent to make good the erosion of academic pay.

The allocation of funds for the coming academic year has apparently been made in the light of universities' accounts of how they plan to adjust to falling budgets. The grants committee is apparently planning to keep back some £20–30 million of the total government grant to finance the more interesting of universities' intended innovations. The new letter to universities pleads, however, that universities having to reduce costs should not take the knife to easily eliminated but academically important minority departments.

The committee has also shared out among its dependent universities the annual government grant for equipment and furniture, fixed last month at £83.6 million. While the Department of Education and Science said last week that the grant is "consistent with the aim of maintaining standards . . .", the grants committee seems strongly to hold that the grant is at least one third too small.

For the more distant future, the grants committee seems to expect that there will be a return to "level funding" after the present contraction is over in 1983–84, but does not know whether the provisional budget for 1984–85 published in the government's expenditure white paper in March will be adjusted upwards if inflation exceeds the supposed 5 per cent a year.

The grants committee itself plans to spend much of the coming year studying possible changes in the social function of universities, especially in continuing education. It remains unclear what will befall those universities which fail to meet the grants committee's targets for reduced student numbers by the end of 1983–84. The sentence in last year's letter suggesting that universities failing to meet their targets would be penalized is not echoed in those sent out last week, but the committee is apparently guessing that if the government should be disappointed with the universities' performance, and should cut the total budget by the extra cost of student maintenance, the budgets of the universities responsible will also be cut.

London medical teaching

Merger fever

While the rest of the University of London continues to agonize about its future, the undergraduate medical schools are at last beginning to implement a plan designed to save 10 per cent of the university's medical education bill by 1983–84. The outlook for dental education also looks brighter since the five dental deans recently agreed to move the school at the Royal Dental Hospital from its premises in Leicester Square to one of the university's four other dental schools. But the future of the postgraduate medical institutes, whose finances have been particularly badly hit by the shortfall in the number of overseas students, will not be tackled until July.

After almost two years of often bitter wrangling, the undergraduate medical schools, collectively the largest source of trained physicians in the United Kingdom, finally agreed on a plan at the end of last year. The dispute began after a committee chaired by Lord Flowers, rector of Imperial College, recommended at the beginning of 1980 that the university's 34 medical and dental institutions should amalgamate into six large conglomerates.

That debate was overtaken by events. The government's announcement at the end of 1980 of large cuts in university education concentrated minds. The plan adopted was designed to increase opportunities for pre-clinical students to choose between medical and multi-faculty schools, and provide access to certain major disciplines, clinical pharmacology, therapeutics and community medicine.

Three of the medical schools, those at the Royal Free, St George's and St Mary's hospitals, are to remain much as they are. The others are to form some type of association either with another medical school or with a multi-faculty college. Thus the medical schools of Charing Cross and Westminster hospitals are to merge. So too are those at the Middlesex Hospital and University College. The schools at St Thomas's and Guy's hospitals are to form a united medical school next autumn and those at St Bartholomew's and the London hospitals are to work towards formation of a joint school. The school at King's College Hospital is to be administered from King's College in the Strand.

The outstanding problem is whether the plan can be implemented in time to make the necessary savings. Schools that must merge will be combining courses, departments and administrations and reorganizing accommodation. St Thomas's and Guy's hospitals, however, will retain their separate schools but merge administration.

The merger of the London and St Bartholomew's schools will take longer. The promise by the University Grants Committee to finance new accommodation for the joint school at Queen Mary College, a multi-faculty institution,

still stands. But the grants committee is now looking for existing buildings which may become available when Queen Mary College has itself trimmed its operations to match its reduced grant.

The reorganized medical schools will be expected to maintain their aggregate student population. But the reorganization alone will not by itself yield the necessary savings. So student:staff ratios are to decline from the present 1:7.4 in pre-clinical studies to 1:10 by 1983–84 and from 1:6 in clinical studies to 1:7.

Judy Redfearn

Polish sciences

Nothing to read

Poland's endemic hard-currency problems are posing a major threat to Polish science. The purchase of Western scientific journals is virtually impossible, and according to the Warsaw daily *Zycie Warszawy*, last year no subscriptions were paid to foreign suppliers at all, so that by October the country had run up a debt of about US\$8 million for journals supplied against invoices.

This year, some \$5 million have been allotted for the purchase of journals, but this is only half the quota for 1980 and less than 20 per cent of the 1978 level. Polish scientists have had to resort to various stratagems to keep up with their reading. Photocopies of *Current Contents* were displayed on the noticeboards of institutes and universities and scientists requested a photocopy of articles they required from the Academy of Science or else through interlibrary loan. Martial law, however, meant that very tight security controls were imposed on photocopyers, lest they be used for the production of protest leaflets.

At the same time, their other main source of new publications — offprints and duplicate copies of journals requested from foreign colleagues — has been considerably reduced. Under martial law, the mails are considerably delayed by the censorship, scientific visits to and from Poland have been significantly curtailed, and many Westerners are apparently disinclined to send material to their Polish colleagues for fear that journals arriving from abroad might attract the attention of the security authorities.

So far, little has been done abroad to relieve the situation. The British Council has allotted £25,000 for the purchase of journals for Polish academic institutions; in the United States, however, the view is by no means unanimous that aid would be proper until martial law comes to an end.

But to Polish scientists the situation is a matter of intellectual survival. Letters to Western colleagues emphasize that without an emergency supply of journals to tide them over the current crisis, Polish scientists will rapidly fall behind the world scientific community, and catching up, when dollars become available again, will be virtually impossible.

Vera Rich

CORRESPONDENCE

The DNA disease

SIR — This is an account of a disease which has recently attained epidemic proportions. In February 1975 at a meeting held at Asilomar Conference Centre in California, many scientists and the world at large first learned of recent developments which came to be known as the recombinant DNA molecule technique, whereby genetic information initially in one organism could be translocated into another where, with reasonable luck, it might prosper and ultimately find expression. This announcement was followed by a wave of anxiety among the knowledgeable. It was confidently forecast that among the new chimaeras which might thus be generated there would be some that were malevolent. New toxic gene products would be let loose in the world and organisms which had, for millennia, lived in friendly symbiosis would be rudely ejected from their niches by novel and hostile forms.

The assembled scientists at Asilomar therefore agreed to conduct their experiments under severe constraints of biological and physical containment. The intent of these regulations, drafted as "guidelines" by the Recombinant DNA Molecule Program Advisory Committee of the National Institutes of Health, was to minimize the likelihood of any of the foreseeable catastrophes.

It is now quite generally agreed that the anxieties which were initially generated were without much substance. Curiously, however, the one serious damage to our ecosystem which has now been observed to occur as a result of application of the recombinant DNA molecule technique was totally unanticipated in 1975.

The problem has arisen as a result of the discovery that some of the gene products derived from recombinant DNA experiments commanded a high market value. The gene which was enhanced was that for venality and the unanticipated gene product was money — sometimes in the form of shares in an entrepreneurial company — sometimes in the form of stock options. This gene product to which many investigators had not previously been exposed might well have been contained had the experiments been conducted under appropriate physical containment such as that in a bank vault. However, the new disease proved to be quite contagious, spreading rapidly even to the administration of the institutions in which these scientists were housed. With great eagerness, everyone wanted a piece of the action.

Among the symptoms of the disease most prominent has been a deterioration in communication, both verbal and written, on the part of those affected. They simply will not tell their friends and neighbours what they are doing or what they intend to do. Both teacher and student have schooled themselves to be close-lipped lest the competitor discover the name of the new product or the means to its production.

Concurrently, a change was noted in the dissertation problems assigned to graduate students. Whereas these formerly always contained an element of new *knowledge*, now the stress is more towards a new *product* and preferably a marketable one. The student may not be assured of what would formerly be

termed an excellent graduate education, but he is more or less guaranteed a well-paid job at the end of the road. In some instances, if the entrepreneurial company is remote from the campus at which the professor is nominally employed, the academic chair which he is expected to occupy may be vacant much of the time. Science gives way to technology, research to development and publication to patent. Lip service, of course, is still paid to basic research, but clearly the product is the thing. For what is an entrepreneurial company without a product?

The prognosis for this epidemic is, at present, unfavourable. So far no treatment for the disease has been forthcoming; and whereas measures to prevent its further spread can be imagined, no one seems to have the strength or the authority to impose the rigid quarantines that would be necessary. Readers of the *Arabian Nights* may recall what happened when, inadvertently, the genie was allowed to escape from the bottle. Having allowed the venality gene to escape, we cannot foresee how the matter will ever be put right again.

DEWITT STETTEN JR

Department of Health & Human Services,
National Institutes of Health,
Bethesda, Maryland, USA

Turkish rights

SIR — As a foreigner who has studied and taught in Turkey for about eight years, I found your version of Dr Ögelman's case lacking rationalism and credibility (*Nature* 25 February, p.638; 18 March, p.186).

I was a member of the faculty of the Middle East Technical University at Gaziantep during the academic years when the internal political strife and violence on the Turkish campuses and in the streets was at its peak. It is no secret that some of the faculty at our campus, and indeed at every other campus, were openly involved in supporting the extreme right or left. As a matter of fact, during those days it was almost impossible and certainly very dangerous not to take sides, which meant inviting the wrath and enmity of both sides. At our university, where the leftist students and the faculty had the upper hand, anyone trying to be neutral and reasonable was branded as a fascist, which made the foreign faculty members, like myself and other North American and West Europeans, very vulnerable and insecure. My office and classroom were heavily pelted with stones for just beginning a lecture on the date when some leftist student had been jailed or hanged in the past. There were daily incidents of bombing and stabbing inside and outside university campuses and everyone lived in an atmosphere of terror.

Active collusion of a part of the faculty with the criminal elements of both the right and the left frustrated the efforts of the university administration to bring about normalization. The police, who could not enter the university premises without prior authorization from the university, usually waited outside as passive and helpless observers while mobs of unruly students of a majority group kept the other students outside the university grounds.

I am neither familiar with the facts of Dr

Ögelman's case nor is it my intention to defend the policies and/or practices of the Turkish government. It is, however, a known fact that Cukurova University, which was only a couple of hours drive from us, was the scene of repeated violence and had to be shut down frequently. You state that "Dr Ögelman has been prosecuted not because she is a physicist but because of her part in an organization intended to secure rights for women in a society in which these have recently been denied".

I am afraid that the basis of your above statement as well as your advocacy for the cause of freedom for the Turkish scientific community need to be re-examined objectively and impartially. First of all, the rights of the Turkish women are solidly entrenched in the constitution. I have made several inquiries here and no one seems to know what rights the Turkish women have been denied recently and how Dr Ögelman's organization is planning to restore those rights. In this connection, it would have been helpful if you had included the name of that organization also. From my own experience and knowledge as a resident of Turkey for almost eight years, I have no hesitation in saying that the Turkish women enjoy more rights and have far greater opportunities for advancement than the women of North America.

As a scientist living and working in a free society, I appreciate and support your efforts in publicizing the plight of fellow scientists under oppression, but such incidents must be presented along with credible evidence which, in my opinion, has not been done in Dr Ögelman's case.

M.H. SADAR

Middle East Technical University,
Gaziantep, Turkey

SIR — Your article "Turkish illiberality" (*Nature* 18 March, p.186) is a completely erroneous interpretation of the liberality in Turkey today. Being the co-author of the research paper published in the same issue of your journal (p.231), I must protest strongly at your misinterpretation of the situation of people with limited freedom in my country. Above all, the fact that you equate the Turkish martial law authorities with the Polish and Argentinian martial law authorities has driven me to think that your long established, serious and scientifically respected journal is taking advantage of its position by resorting to cheap politics.

As you should know, Turkish women gained their rights in 1923 under the great leader Atatürk. The women's organization mentioned in your article has attempted to give a misleading impression of the Turkish community, which consists of wholly liberated women. Scientists are human too; they can commit wrongs and rights, and can be condemned or set free.

The martial law authorities in Turkey have not limited liberality and democracy, but on the contrary have created an atmosphere of pleasantness and friendship between people who were enemies before the present regime took power. Above all, their existence has eliminated anarchy and its fatal consequences.

SELIM KAPUR

Adana, Turkey

SCIENCE IN WEST GERMANY

Discovery and disappointment

THIS year is a turning point in the development of science in West Germany since the Second World War. For one thing, this will be the first year in which government support for scientific research will not increase in real terms. For most agencies, the shortfall is not serious. In deutchmarks, indeed, budgets will be bigger, perhaps by four per cent. If inflation turns out to be six per cent, the real decrease will be a mere two per cent. But inflation could be greater than that, while, as people elsewhere know, official retail price indices are not an accurate guide to the cost of scientific work.

The budget cuts, although unimportant in themselves, are nevertheless symbolic of questions that have arisen in many minds. In the past three decades of heady prosperity, both the federal and regional governments have backed research generously, and for two reasons: the restoration of German scholarship is as necessary as the restoration of the economy and then, of course, science is an important source of innovation and thus a kind of guarantor that the economic miracle will not fade. So if even the West German economy can be driven into recession, may it not have been a miscalculation to suppose that investment in research would keep economic growth alive? The logic is not very sound, but the question, once asked, cannot easily be suppressed.

To politicians, the question takes the form "Are we getting value for all that money?" Their officials are responding with an energetic campaign to assist the process of "technology transfer". A few spectacular successes could make future budgets safe. But the question echoes another which the scientific community in West Germany seems also to be asking: How well are we doing, anyway? After all these years of effort, why is the United States the place where most of the interesting discoveries are made? Is something wrong?

The most surprising impression left by talks with a variety of scientists and officials is the tentativeness of science in West Germany. People seem to spend an alarming amount of time looking over their shoulders or trying to devise criteria for telling how well they are doing. (Nobel prizes per head per year? Mentions in *Science Citation Index*?) In reality, such lack of confidence is entirely inappropriate. West Germany is not merely crammed with scientific enterprises of various kinds, many of which are internationally known, but the sheer scale of the West German enterprise is breathtaking. Yet even if the state of mind is paradoxical, the reasons why it has arisen may be of absorbing interest.

The brief survey of the state of science in West Germany that follows must not be mistaken for a catalogue. It is based on talks with officials of the federal government in Bonn and a string of visits to universities, laboratories and institutions at scattered centres as well as on the lavish use of the telephone. One objective is to investigate an interesting phenomenon in a manner that may interest readers. Another is the hope that it may be easier in future for *Nature* to do justice to an important part of the international scientific community.

As will be seen, much of what follows is concerned with the mechanisms by which public funds are channelled into research in West Germany. For all kinds of reasons but not least the interaction between the federal and the *Länder* governments and the federal government's constitutional compulsion to delegate decision-making to virtually autonomous bodies such as the Max-Planck-Gesellschaft, these mechanisms are more interesting than almost anywhere else. One consequence is that part of the scientific establishment has been able to capture part of the government's machine, and to use it itself.

Especially in these circumstances, why should there be such a general air of self-conscious uncertainty? (One explanation is that the responsibility is almost too great, but few agree with that.) The first thing to say is that these doubts crop up only in places where the objective is basic research, and where people *might* hope to win Nobel prizes even with the restricted definition of science included in Nobel's will. The people in the engineering school at Aachen know they are doing a unique job superbly, and have no recognizable self-doubt. (Chasteningly, one of them also asked "What is this journal *Nature*?")

Nomenclature

THE Federal Republic of Germany (*Bundesrepublik Deutschland*) is referred to throughout as West Germany so as to avoid the use of some set of initials (for example, FRG) that does not translate into German. The German mark (abbreviated as DM) is the unit of currency except when inappropriate. DM1 = £0.24 = \$0.43 approximately. People's formal German titles are abbreviated by the omission of references to first degrees (for example, *Dipl.-Ing.*) and by the use of one or other (but not both) of the titles Professor and Dr. Place names are given in the English form when the German names cannot easily be pronounced by English speakers (for example, Munich, Cologne) but Hannover is spelled with two ens, as it should be.



So does the self-doubt have something to do with West Germany? That would not be a surprise. Although well over half of those now living in West Germany were born after the end of the Second World War, the economic miracle has tended to obscure the plain truth that West Germany as it now is was cobbled together by the three Western occupying powers in the late 1940s, became a fully sovereign state only in 1955 and gave up all hope of unification with its other half only in the late 1960s. And there remains West Berlin as a reminder to all who care to notice that the problem to the East was never resolved as intended at the Potsdam conference in 1945. As it is, three hours' driving (West German style) will take you from the Dutch border at the Ruhr to the eastern border near Braunschweig. From Göttingen, further south, you can walk to the border and back within the day. And if such circumstances fail to remind the young that West Germany is a living piece of suspended history, like a fly in amber, there are always people ready to remind them. One young woman in a Hannover restaurant asked why she had *still* met so much rudeness on a recent visit to Britain. Who knows how to quantify the effects of this on people's confidence at the bench?

More particular versions of this question inevitably arise. What for example were the consequences of the exodus from German universities in the 1930s? And of the Catch-22 trick that in the 1930s encouraged public servants such as university teachers to join the Nazi Party and then, in 1945, denied public service to former Nazis? The result was that the post-war cohorts of undergraduates, now of an age to be laboratory directors, were mostly taught by people who had been unwillingly conscripted into military service. Again the importance of this effect cannot be quantified; the pages that follow will not

attempt to answer the implied question.

One startling comment on this conundrum, from an older scientist, is nevertheless worth recording. The exodus should not have mattered, the argument goes. For the people who left during Hitler's time, Einstein and the like, were people who had been attracted to pre-war Germany from countries such as Switzerland, so that their disappearance mostly to the United States should in eugenic terms be strictly irrelevant.

Historically, and culturally, the first half of this century may come to seem an irrelevancy. For can it be simply a coincidence that West Germany has finished up a latter-day replica of what Germany seems always to have been — a confederation of autonomous states, as in the Holy Roman Empire of the thirteenth century and the German Confederation that followed Napoleon's defeat? Certainly neither Hamburg nor Munich now would have it otherwise.

Other manifestations of historical continuity keep cropping up. The past decade's spate of social legislation? Merely an extrapolation of the Weimar Republic's attempt to codify the liberally-paternalistic practices of the mediaeval German princes and their successors, the joint-stock companies of the nineteenth century. Legalism, obsession with laws and their interpretation? But that's straight from the Romans, and anyway you cannot feel free until your freedom has been defined. The tendency towards ideology (purpose shaping action) that prevents those who hold to the concept of the interdependent society from breaking into each other's cars but which tempts a small minority along the Bader-Meinhof path? If Calvin's reformation (when Geneva was still part of Germany) caused such trouble, it could not now be seemly to accept as colleagues people whose motives are misguided, whatever their other virtues (see page 264). And scholarship? Even now, in 1982, few can take up that subject without referring to Wilhelm von Humboldt, the founder (in 1810) of the University of Berlin, who at the same time put out the then-liberal and now supposedly-effete message that good research begets good teaching. Evidently the Third Reich might never have happened. And the West German universities have splendidly played their part in fostering this sense of historical continuity.

But for how much longer? It is clear that opinions in West Germany are deeply divided about the wisdom of what has been done to the universities in the past decade or so. Inevitably, the pessimists are more vociferous than the optimists, but they seem also to have the stronger case. So no apology is needed that much of what follows reflects the anxieties of those who are alarmed at the consequences of reform.

This survey has been compiled by John Maddox with assistance as indicated.

Will the miracle come back?

WHATEVER happened to the West German economic miracle, the phenomenon by which in the 1950s Chancellor Konrad Adenauer and his economics minister, Ludwig Erhard, arranged that West Germany should become the most prosperous of all the states of Western Europe? The most comforting answer is that the economic miracle is still there, just waiting for the long recession to end.

This is probably half true. Economic growth and large trade surpluses persisted throughout the 1970s, while other Western economies were already faltering. Only in the past two years has the growth stopped. Unemployment (once negative in that West Germany in the early 1970s relied on an estimated 2.3 million "guest-workers" for its labour force) had begun to rise in 1973, and is now heading for 2 million. And inflation, somewhat exaggerated by the West German retail price index at an average of 6 per cent a year in the 1970s, has now begun to increase. At least part of the trouble is that West Germany has at long last been affected by the stagnation of international trade in the manufactured goods which constitute some 47 per cent of the country's export trade.

Nobody, however, believes this to be the whole story. For one thing, there is the cost

of oil and natural gas, almost all of which has to be imported. Although conservation measures have had a substantial effect on petroleum imports (down from 98 million tonnes a year in 1974 to just over 90 million tonnes a year now), the cost of oil and gas is between a sixth and a fifth of West Germany's import bill. This charge on the economy is not going to go away.

People in West Germany are more alarmed, however, by what seems a sinister threat to future prosperity — the challenge from Japan. The days have long since gone when Volkswagen's beetle swept the world. Now the beetle's successors have to compete in the export markets with cheaper but still well-engineered products from the Far East. The same is also true in electronics. And for other reasons, the West German chemical industry — the other foundation of the post-war export trade — has faltered, financially shackled by expensive investments conceived of when economic optimism was the order of the day. So everybody is convinced that there must now be a new period of creative innovation in West German industry. "Technology transfer" is the slogan. Science may be one of the beneficiaries.

Much less often, people also worry about the possible consequences of the past

Briefing

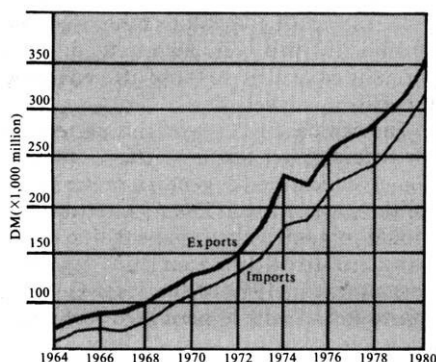
WEST GERMANY is the quintessential federal state. Its existence springs from the decision of the three Western occupying powers (France, the United Kingdom and the United States) in 1947 that a measure of self-government should be permitted in the west of the country pending agreement on German unification. The "Basic Law" (*Grundgesetz*) adopted at Frankfurt in 1949, for practical purposes the constitution of West Germany, reflects the insistence of the occupying states that political power should as far as possible rest with the regional (*Land*, pl. *Länder*) governments. (West Berlin is an eleventh *Land*, but has a special status.)

The basic law provides a complicated system of checks and balances by which the powers of the federal government are constrained. The power to take on tasks (such as research) not specified by the basic law requires a formal treaty between the federal and the *Länder* governments. The second chamber (*Bundesrat*) of the federal parliament consists solely of representatives appointed by the *Länder*. The federal constitutional court (*Bundesverfassungsgericht*), based at Karlsruhe, interprets the constitution on demand, and can overturn legislation deemed unconstitutional while also considering, for example, appeals by students against examination results.

The partition in 1945 of Germany and its consequences (east-west migration) have left West Germany with just over two-thirds of the total area (excluding the parts of Germany transferred to Poland in 1945) but four-fifths of the population (now 61 million).

The post-war history of West Germany has been shaped as much by the economic miracle of the early 1950s as by the almost continuous wrangle about East-West relations. Starting from an admittedly low base, for the best part of a decade the West German economy grew faster than any other in Western Europe. Now the Gross National Product is close on US\$10,000 per head of population, close to that of the United States.

Since 1969, the federal government has been formed by a coalition of the Social Democrats (SPD) and the Free Democrats (or liberals), with Willy Brandt and Helmut Schmidt as successive chancellors. Now, however, there are signs that the coalition's hold on the federal government (and the cohesion thereof) is weakening. The Chancellor has had trouble within his own social democratic party on nuclear policy (civil as well as military), while the coalition has begun to lose control of some *Länder* governments. The election in Hesse (capital Frankfurt) in September is likely to be crucial to the coalition's future (and to its capacity to govern effectively between then and the *Bundestag* election still two years away).



The increase (in actual values) of West Germany's exports and imports. The major exports are all types of machinery, motor vehicles, electrical engineering and chemical products. Major imports are food, drink, tobacco, petroleum and natural gas.

decade and a half of social reform introduced by the Social Democratic Party (SDP). Certainly the past few years have seen a substantial increase in social transfer payments by the federal and *Länder* governments for such things as pensions, student support and unemployment assistance (and the high cost of these statutory payments when tax revenues have been reduced by the recession is the

immediate cause of the economies now being enacted throughout public administration). But there is no sign that the SPD government's reforms have in any way impaired the efficacy of the market economy which has been the engine of economic success in the past three decades. Thus the statutory extension in 1976 of the rights of workers to participate in management decisions (at a time when even a British Labour government failed to make headway towards similar objectives) is said even by Christian Democrats to be but a continuation of a tradition going back, in West Germany, to the 1920s.

But may not people's attitudes have changed? The economic miracle was a heroic time for West Germany. People rose to the challenge. Now, some fear, affluence has made the younger generation work-shy, from which point of view the activities of the "greens" (politically active environmentalists) is akin to sabotage of the West German dream. Such gloomy after-dinner musings are probably mere speculation. That they are offered at all as serious contributions to the question of what the future holds is a measure of the extent to which the economic miracle lies in the past. □

Universities reformed to death

By spitting out a peppermint in a dental surgery, does a dental student demonstrate such an ignorance of simple hygiene as to be unqualified for his profession? Last year, after an angry scene with such a student, a member of the dental faculty at Munster took this view, and said that a final examination should be retaken. But the local appeals court has now decided in favour of the student.

This solemn affair illustrates one of the common complaints of academics in West Germany. Legal interpretations of the public duty of academics (who are public servants) take precedence over research and teaching. But of the thousands of suits brought against the universities each year, most come from would-be students seeking to prove that they have been wrongly denied a place.

So what has become of the "Humboldt university", that community of scholars willing to share their learning with anybody who chose to take part? The embittered say that the classical German university has been killed off by the sequence of reforms to which the West German system of higher education has been subjected in the past fifteen years. The reformers agree that the system is still in turmoil.

The underlying trouble is that West Germany has sought to reconcile several irreconcilables — the principle of open access to any university in the country, the doctrine that all universities are equal, the practice that universities are run by the ministries of culture in the *Länder* in which they happen to be sited and the

phenomenal increase in the demand for higher education in the past twenty years. Add the West German conviction that the law is the law is the law, and the plain fact that the reforms, consisting as they do of formal agreements between the federal and the *Länder* governments, are public legal documents, and you have a recipe for muddle, even chaos.

Historically, this mess was preordained. After the twelve years of incivility that ended in 1945, what can have been more natural than that the few surviving academics and the army of their would-be successors should have set out to recreate the Humboldt university, with all its blinding virtues and glaring faults?

The principle is admirable. The university is a community of scholars supported by the state (*Land*) as if it were an opera company. The scholars or professors (*Ordinarien*, sing. *Ordinarius*) are the university but each year they elect one of themselves (the *Rektor*) to be their head. As public servants, their duties are spelled out (for example, to lecture eight times a week) but they negotiate their salaries with the *Land's* appointed bagman in the university, the Chancellor. He and not the *Rektor* also decides each professor's allocation of assistants, research expenses, janitors and capital costs. Students do not explicitly enter these calculations. The bright or pushy become unpaid laboratory assistants ("learning through research"). The others move on elsewhere, looking for something more congenial.

This system, which made possible the

flowering of German scholarship at the end of the nineteenth century, is obviously open to abuse. Well-favoured professors may acquire delusions of divinity, and may tyrannize their assistants. And since even among scholars, rivalry and even jealousy may from time to time occur, professors in related fields and their respective entourages, organized into separate institutes, may occasionally behave like warring empires.

Great men and good universities usually managed to avoid such dangers. But the universities recreated after the Second World War were faced with a rapid growth in the numbers qualified to be students. By 1960, it was plain that the then-existing universities could not be expanded indefinitely, and that new institutions would be necessary. With Nordrhein-Westfalen in the lead, and with the promise of financial assistance from the federal government, the *Länder* set out to create new universities more or less in the image of the old. But the pace of construction was insufficient, and the replication of universities in the existing pattern could not meet the needs of society, let alone of students.

So what was to be done? By the mid-1960s there was a fierce argument between those represented by Professor Ralf Dahrendorf (then at Cologne, now director of the London School of Economics) who argued that there should be institutions equipped to provide vocational tertiary education (and shorter and more structured courses all over) and those who sought a more radical change in the structure of the university while preserving the cherished notions that all universities are in principle equal and that qualified students may study where they like.

The argument, unfortunately, did little to help the universities overwhelmed by students, some of which began to operate a *numerus clausus* rule — students should be turned away if there were already too many of them in the university or some part of it. This offence against the doctrine of free access was held to be an infringement of people's constitutional right to follow the profession of their choice. The operation of a quota system now, in fields such as medicine and veterinary medicine, is one of the chief sources of litigation by would-be students.

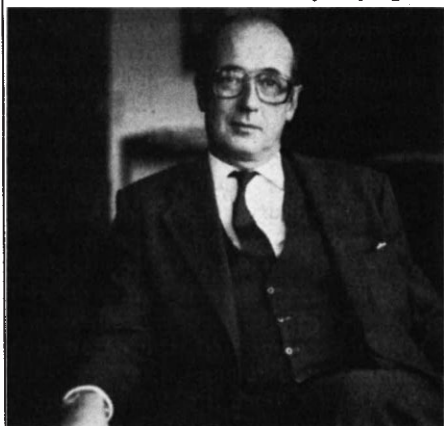
The second wave of expansion in higher education that began in 1970 appears to have given something to both parties in the earlier argument for reform; technical colleges of various kinds, traditionally means by which the graduates of non-Gymnasium high schools acquired a vocational education, were enlarged, upgraded and called *Fachhochschulen*. And the new universities established after 1970 (often built around pre-existing technical or teachers' colleges) were "comprehensive" in that they offered courses of frequently vocational study,

A conservative opinion on reform

THE universities are intrinsically conservative, so how can "reform" imposed from outside fail to damage them? This was the gloomy lament of *Rektor* of the University of Munich, Professor Nikolaus Lobkowicz, on the day last month when he had just handed in his resignation to the Bavarian government after being voted out of office.

A touch of bitterness would in the circumstances have been forgivable; that university rectors should be elected every four years is laid down in the federal reform law for higher education. But that suspicion is too dark. Professor Lobkowicz is a political scientist born in Czechoslovakia who has spent most of his working academic life in the United States. His description of himself as a true conservative is relevant.

The University of Munich is the biggest in West Germany, with 45,000 students or thereabouts. Bavaria is the stronghold of the Christian Democratic Union and, Lobkowicz thinks, the *Land* made a tactical mistake in 1969 by trying to



Lobkowicz — eloquent on reform

preempt the federal law then being hatched by making one of its own. Bavaria overlooked its own long-standing tendency towards "preposterously perfect" legislation.

Legalism has run riot. In one recent year, the university awarded 1,100 doctoral degrees but had to fight 1,300 court cases, most of them brought by students contesting examination results. Occasionally, the university takes the government of Bavaria to the Constitutional Court in Karlsruhe.

The bureaucracy, the *Rektor* says, is palpably a pain; the damage done to academic standards cannot be as easily assessed. But surely the old system, in which holders of a university chair (*Ordinarien* in the old nomenclature) were treated as gods in their departments, was capable of corruption? So what? is the surprising answer. "Who says that corruption excludes excellence?"

The most serious of the present dangers in Professor Lobkowicz's opinion is that the new system for appointing people as professors of one of the Western world's

great universities will ensure that they are "smooth" people, first of all electable and only secondarily capable of scholarship. The drill now is that the senate instructs the *Rektor* to submit a list of three nominees for each professorial appointment to the *Land* government, in order of the "soviet's" preference. (Students and other ranks are represented on these committees, but professors have a majority.)

The minister knows that there will be a row if he fails to appoint the first name on the list, but apparently there have been occasions when a discreet telephone call has persuaded him to take the risk. One of Lobkowicz's own regrets is that he failed to persuade his fellow academics to appoint as an honorary professor a distinguished Marxist philosopher "with whose every word I disagree" but who might have been good for the university. Reform, says Lobkowicz, has made the world safe only for the safe.

The result, he says, is that both scholarship and the scholarly professions have been debased. The great teachers of the old days have been replaced by people on the hunt for material with which to embellish their *curricula vitae*. And the days have long since gone when it was reckoned better to be a university professor than a bishop. So university teaching has become less attractive to bright people, those left are reluctant to welcome colleagues who may be brighter than themselves — and the brightest students are in any case persuaded to opt for courses of study to which entry is restricted, medicine for example.

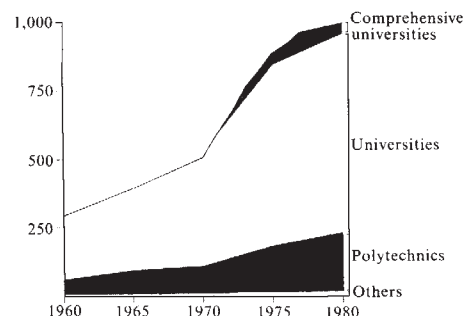
On the state of West German science, Lobkowicz is more puzzled than dismayed. Nobel prizes or the purchase of foreign patent rights are poor criteria of success, he says, while the prevalent academic convention to despise the popularization of scholarship has removed academic scientists from intelligent appraisal by their fellows. He notes the growing tension between university teachers and those working in Max Planck institutes, who have more time for research. He agrees that young people returning to West Germany from a successful spell in, say, the United States tend to lose their sparkle once back at home.

The explanation? The bureaucracy engendered by the reform. Yet Munich has been lucky in its minister of culture — it has dutifully "integrated" the *Pädagogische Hochschule* and only one department has been "ruined" in the process.

Why not, then, reform the reform? The outgoing *Rektor* is despondent even about that. For an amended law would be even more detailed than the present, allowing more scope for legalism. But Lobkowicz says that he differs from his colleagues elsewhere in this opinion and he insists that his is a conservative view. It is, however, eloquent and influential.

used instructional methods other than the formal lecture yet awarded degrees formally equivalent to those offered by the pre-existing universities.

The cap has been set on this pattern by the federal government's "frame law" on higher education, a general prescription for the ways in which *Länder* governments should organize their universities made constitutionally possible by the amendment in 1969 of the West German constitution, which permitted collaboration on "common tasks" between the federal and *Länder* governments on



Student registration in higher education in West Germany from 1960 to 1980 (in thousands).

matters previously reserved to the latter. One objective of this tortuous piece of legislation is the removal of the opportunities for abuse in the classical German university. Departments rather than professorial chairs (*Lehrstühle*) were decreed to be the "basic organizational units", *Rektors* were to be elected for four years rather than one, staff vacancies were to be advertised, and so on.

The crucial and controversial part of the frame law, however, is the declaration that

... the different types of institution of higher education shall be brought together to form a new system of higher education. Institutions shall be extended or merged to become comprehensive universities or, while retaining their legal autonomy, shall be linked together by the establishment of joint bodies to form comprehensive universities. Where it is not, or not yet, possible to establish comprehensive universities, cooperation between institutions is to be assured.

The zeal with which these principles have been prosecuted varies from *Land* to *Land*. Although the deadline for decision specified in the act was 1979, the system is still in flux. Observers from outside must marvel at the confusion that results. Here is one list of what seems to be awry:

● A university cannot match student registration to its capacity to teach unless the *Land* government has formally declared a shortage of capacity, in which case only the Central Office for the Allocation of Study Places can decide which students shall be taken in. In practice, quotas apply principally in medicine and related courses. The law specifies that two-thirds of the available places should be allocated according to

grades in high-school leaving examinations, but the number of years spent waiting for a place should count in the allocation of the remainder.

● The time spent by universities and their academics in providing information about the way they spend their time (essential if a university is to defend itself against law suits brought by students who argue that they have been turned away when they could have been taken in) is an intolerable intrusion that makes the "effort reporting" required of grant-holders in the United States seem benign.

● While entry to restricted courses is to some extent determined by school-leaving grades, the recent reform of the *Abitur* system makes possible a degree of specialization at school, but there is no means of linking that with the course chosen at university; whence the complaint that school-students plump for easy options when their real aim is to enter a medical school.

● The attempt to modernize the content of university courses, and to ensure national uniformity in deference to the conviction that a degree is a degree (or that all universities are equal) and to ensure transferability from one place to another has the predictable effect of increasing the duration of students' courses, now more like six years than the minimum four. (Students' grants, a liability chiefly of the federal government since 1972, run out after five years.) Yet students' preferences for the older universities suggest that they do not regard the universities as equal, so the newer universities are, through no fault of their own, under-used.

The consequences of all this for the conditions of the research enterprise are only indirect. The mechanisms for financing research in universities are enlightened (see below), and almost entirely in the gift of the research community itself. But in the universities that remain popular with students, the teaching load has become intolerable (research during vacations only), and the nature of academic life has changed in such a way that people are likely to find the Max Planck institutes even more seductive than they already are. Doubts persist about the way in which students are being taught.

The past few years have, however, seen a more immediate problem. The federal and *Länder* governments, linked financially together by the taxation system, are being forced to live within their means. In many places there is a moratorium on filling academic places, and a 7.5 per cent reduction of all public posts is likely by 1986.

In Nordrhein-Westfalen, the spearhead of educational expansion in the 1960s, the problem is more acute. By being first in the movement to establish comprehensive universities, the *Land* has saddled itself with educational facilities still under-used, as well as with institutions such as the great medical school at Aachen (see page 267)

whose future must be problematical. The result is that the word went out from Dusseldorf (the state capital) at the end of March that there must be reductions of the scale on which the traditional universities operate. In a form reminiscent of what has been happening in Britain in the past few years, the Minister of Culture has recommended that this or that department must be closed. The University of Bonn, now bursting at the seams with 35,000 students (including 5,500 law students) in buildings fit for half that number, has been told that it must lose part of its teacher training pro-

gramme, and its institutes of egyptology and Scandinavian studies. Dusseldorf's immediate target is to save 400 jobs at Bonn. Nobody knows how many of those posts are intended to finish up at places such as Aachen. Indeed, it is still possible that the overcrowded universities will be able successfully to resist what Dusseldorf has in mind. If the issue is settled before the mid-1980s, when the falling school rolls will have worked their way through to higher education, giving some relief to the overcrowded universities, everybody will count himself lucky. □

Where to get research grants

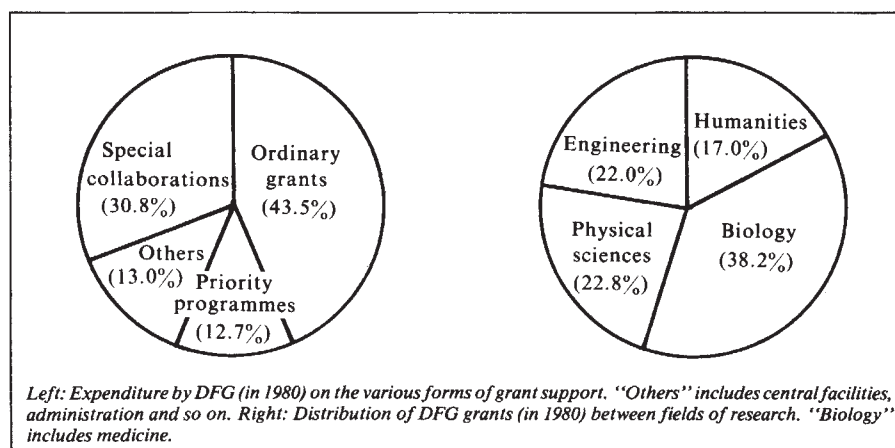
PLURALITY is most academics' defence against the peer review system, but not in West Germany. For there is just a single agency for supporting research in higher educational institutions — Deutsche Forschungsgemeinschaft (German Research Society) or DFG. Curiously, however, this single organization is not the monolithic enterprise that might be feared; grant applicants speak well of what it does, even if university administrators complain of having to sign several identical pieces of paper for each grant application.

Part of the explanation for the respect accorded to DFG is historical. There has been a device of some kind for helping academics to carry out research since 1920, when Max Planck and Fritz Haber persuaded the then *Reich* to put money into such an enterprise. After the Second World War, DFG was formed by a merger of two similarly intentioned organizations as the result of a treaty between the federal and the *Länder* governments.

The legal constitution of DFG also helps. It is not a government agency but the strict equivalent of a "not-for-profit" organization in the United States or an operating charity (a company limited by guarantee) in the United Kingdom. And those responsible for its operations are not people but a motley collection of legally autonomous academic enterprises — many (but not all) of the universities, some (but only a few) of the national research centres

and a sparse sampling of learned and scientific societies. The result is that even though the funds for DFG's operations come from the federal government and the *Länder* governments, which are all represented on various high-level committees, these same committees provide such a complicated system of checks and balances that the potential beneficiaries of DFG have a real sense of making policy, particular and general.

At the same time, DFG has many of the functions of what are elsewhere known as national academies. Thus it pays the West German contribution to bodies such as the International Council of Scientific Unions, looks after the exchange of scientists with other countries in Europe and elsewhere, worries about scientific libraries (and such questions as computerized information services), carries out studies at the behest of government and runs the "Heisenberg programme" — West Germany's device for helping people who would in other times walk straight into academic jobs but who are now, in a period of relative stagnation, kept waiting on the sidelines. It differs from a learned academy, however, in the scale of its operations — the budget is close on DM900 million — and in not electing people to any fellowship. Naturally, German culture being what it is, DFG looks after the whole of scholarship, both Protestant and Catholic, theology included.



Another Catch-22?

THE West German government, a great believer in economically counter-cyclical devices, was among the first to introduce (in 1978) a scheme for catering for younger scientists for whom there would in normal times have been empty academic posts, but who in present circumstances are likely to be forced out of research. How well is this Heisenberg programme working?

By the beginning of 1982, 246 people had been awarded fellowships, which can run for five years. The scheme was devised by the West German Rectors Conference, is supported financially by the federal and *Länder* governments, and administered by the DFG.

Those eligible for support must be qualified (by means of the *Habilitation* process), for appointment as a tenured

university professor. One striking proof for this necessity is the frequency with which visiting cards refer to this qualification, unknown outside West Germany.

However, the DFG is apparently not able to spend all the funds at its disposal for this purpose — enough for 150 new fellowships each year. The problem is that selection committees are anxious that those awarded Heisenberg fellowships should be people who could, without disgrace to themselves or anybody else, move into a university post should one become vacant. But those are also the people who are likely to be snapped up by Max Planck institutes, industry and, even in these straightened times, the universities.

What seemed, only a few years ago, to be an imaginative solution to a widely recognized problem has thus turned out to be another Catch-22.

As a grant-making organization, DFG does business in a variety of ways. At one end of the scale is the standard procedure by which academics can apply for research funds to employ research assistants, to travel abroad, to be freed from teaching and research for a year and even to prepare (over a period of no more than two years) for qualification as a full university professor (*Habilitation*). DFG spends close on half its budget on these activities, and makes more than 5,000 grants a year with an average cost of about DM80,000 each. Half of the cost is met by contributions from the *Länder* and federal governments.

As in Britain, grants of this kind are made on the assumption that university applicants already have access to the essential tools of research. Hitherto, the *Länder* governments appear to have been generous in this respect, partly from regional pride, partly because well-equipped universities are better able to compete for centrally administered funds. But DFG is alarmed at the signs that have become apparent in the past two years that many applicants are no longer able to satisfy their sponsors on this point. With misgivings, DFG is now paying for some equipment that it would previously have expected the university to provide; the fear is that too much of this will erode its capacity for making grants.

Larger projects are financed by different mechanisms. A group of researchers at a university can apply to be financed as a research group, and there is a "priorities programme" that enables groups of academics anywhere in West Germany to collaborate on a research topic considered by DFG to require special attention.

West German participation in the Deep Sea Drilling Project has been in part made possible by a priorities programme grant of more than DM20 million to a research plan coordinated by Dr Helmut Beiersdorf from the Federal Geophysics and Natural Resources Laboratory at Hannover, which

involves some 36 investigators at 14 universities (most of whom have used DFG funds to buy equipment). More recently, nationwide collaborations on this pattern have been set up in gene technology and the mechanical engineering of miniaturization technology.

The most distinctive of DFG's mechanisms for supporting academic research is, however, the scheme for providing long-term grants to university departments prepared to concentrate their research in some specified field. This *Sondersforschungsbereich* programme supports projects as different as the University of Bonn's continuing interest in radioastronomy (see page 274) and a variety of clinical projects scattered through West Germany. Since the beginning of the programme in 1968, about 180 of these special collaborative projects have found their way onto DFG's books. The scale of support appears to range from DM1 million a year or less up to DM12 million a year (for the marine construction project at Hannover), with the average cost at about DM1.5 million. Unlike DFG's other grant-making activities, the costs of this programme are not shared equally by the federal and *Länder* governments but, rather, are divided in the ratio 3:1.

While it seems that DFG has frequently brought such projects to an end, there has been a tendency over the years for the number of current projects to increase. But now DFG is constrained by a recommendation of the Wissenschaftsrat that these projects should not normally last for more than 12 or 15 years. With 40 current projects going back to 1968, the next few years will see rapid change. This is part of the reason why the theoretical mathematics *Sonderforschungsbereich* at Bonn is being converted into a Max Planck institute. Elsewhere, some discreet renaming of research projects may be necessary.

At the Max Planck institutes, DFG operates a formal and stringent system of

invigilation for deciding whether support for one of these special programmes should continue. Every three years or so, a team of people in the field spends two days interviewing the members of each collaboration, raising awkward questions about the inevitable gap between aspirations and achievement. The invigilators pride themselves on being tough.

Broadly speaking, DFG seems confident that, despite this year's interruption, its previously steady growth will soon be resumed. Between 1981 and 1982, the budget grew by just six per cent, the equivalent of inflation, but the prospect is that next year's budget will be only four per cent greater than now — an increase less than the probable inflation rate. The general secretary of DFG, Dr Carl Heinz Schiel, expects that DFG's budget will continue to grow at least until around 1990, when demographic change may imply that the university system begins to shrink.

As an essential component of what would elsewhere be called the dual-support system for the universities, perhaps the most immediate threat is that, as in Britain, regular support for the universities may be so cut back by the *Länder* governments that DFG's grant-making capacity will be undermined. Inflexibility is another difficulty. Because of the different degrees of the involvement of the *Länder* governments in DFG's general and special programmes, the transfer of funds from one part of the budget to another is constrained. Moreover, because new *Sondersforschungsbereich* projects have to be approved in advance by the Wissenschaftsrat, speed cannot be assured nor political interference ruled out.

What seems most conspicuously to be missing from the pattern of DFG's activities is some mechanism for supporting substantial programmes of research by the younger members of academic faculties. The Heisenberg programme (see box) is intended to keep some such people in an academic orbit when they might otherwise be frozen out, but the needs of young and potentially daring researchers seem to fall between the two stools of modest individual support as part of the standard grant mechanism and the much larger programme grants in which large groups of people, many of them senior scientists, are simultaneously involved.

The consequence may be the explanation given by one academic molecular biologist, a member of one of DFG's research groups, for his fatalistic expectation that the next dramatic development in his field would be made by some American group. But why not you? "Well," he said, "our hierarchy is more rigid than theirs, we are less mobile and our communications with each other are less good." Add to that the teaching load, which keeps senior academics away from the bench except during vacations, and you have a recipe for being second. □

A little knowledge

If *wissen* means "to know", then *Wissenschaft* means "knowledge", and since German culture makes no distinction between different branches of knowledge, *Wissenschaft* accordingly includes "science" as one of its English meanings. But this English legend does not correspond with present usage.

A further complication is the use of the prefix *Natur* (meaning "nature") as a qualifier, for *Naturwissenschaft* means "physical science", as distinct from, say, the biological sciences (as in *Biowissenschaften*), but *Naturforschung* appears to mean scientific research of any kind. Confusion is not common, but appears to have led to the common practice of translating *Wissenschaftsrat* as "science council".

That unique institution, made necessary by the federal character of the West German constitution and set up in 1957, has a general influence on the development of the university system and the research enterprise in West Germany. The *Wissenschaftsrat* is a kind of constitutional rubber stamp. Its general assembly consists of two constituencies — one appointed by the federal government and one representing each *Land* equally — with equal voting power. There are also outsiders from universities and business who do not vote. Technically, the council is advisory to the federal and *Länder* governments. Recommendations require a two-thirds majority, which means that the federal government can have its way if four *Länder* support it.

For the first decade and a half of its existence, the council was creatively influential; and even now it would be imprudent of the federal government or one of its agencies to think of doing something new without the council's agreement. Thus proposals that public money should be spent on a new laboratory, or that some new university should be established, are at some stage cleared with the council.

The agenda for discussion has shrunk since the constitutional amendment of 1969 that gave the federal government a role in higher education. Even so, it retains a life of its own. In the past two years, it has for example argued successfully that the *Deutsche Forschungsgemeinschaft* (DFG) should not make long-term programme grants for more than 12-15 years (which advice appears to have been taken seriously). The council was more recently influential in the decision that the new Alfred Wegener research centre for polar research should be located at Bremen rather than at Kiel.

The most accurate translation of the council's German name may therefore be "the council for the politics of scholarship".

Aachen's other cathedral

THE great *Klinikum* of Aachen stands in relation to the city at which Charlemagne was defeated as did the opera house to Sydney a decade ago: it is too soon to know whether it is one of the wonders of the modern world, a white elephant or both. But the now-estimated cost of DM 1,700 million of what may yet become the world's most gargantuan teaching hospital has already so cramped the budget of Nordrhein-Westfalen that the repercussions will be felt next October in all the *Land*'s universities from Bonn to Bochum.

Like Aachen's cathedral (probably the loveliest of them all), the *Klinikum* lies in a hollow but towards the west of the city, within sight of the Belgian and Dutch borders. Like all cathedrals, the *Klinikum* is huge, with a usable physical capacity of 130,000 m³ and a gross volume (including air-conditioning plants and the like) of half as much again. If ever completed, it will house 10,000 people, including 1,500 patients, 2,500 medical students and up to 500 dental students. Like many mediaeval cathedral projects, the *Klinikum* has been plagued by subsidence — some parts of it have sunk by as much as 5 cm.

Like any cathedral, the *Klinikum* is the physical expression of somebody's vision — in this case, that of Mr Hans Wertz, once financial controller of the city of Aachen, who, when finance minister of Nordrhein-Westfalen in the early 1960s, appears to have wished on his native city and on the university (the Rheinisch-Westfälische Technische Hochschule) which the *Land* "owned" there, the promise of a building in which physicians could make their dreams come true, together with an accompanying blank cheque.

Although RWTH, as it likes still to be known (see page 275), now seeks to distance itself from the huge cost of the *Klinikum*, at the outset it was a willing accomplice.

This distinguished institution, best known for its contributions to the health and wealth of the West German machine-tool industry, acquired a medical faculty only in 1965, three years before the notion

of the *Klinikum* was hatched. Even academics would have known that most other universities with medical schools could largely finance them from the payments made by the insurance companies with which West German workers are compulsorily insured.

During the past fifteen years of construction, the dream has faded in several ways.

- The hope that the Aachen *Klinikum* could become a truly European hospital, drawing patients from Belgium and the Netherlands as well as West Germany, has been frustrated because insurance companies' payments are no more transplantable now than in the 1960s (and because the Dutch have closed their border since terrorism became rife).

- The discovery that the infective organisms of legionnaires' disease flourish in the humidifiers of air-conditioning plants has made it necessary to modify the design of the large single plant.

- There was a successful prosecution in 1976 of a suit in the West German courts by complainants holding that work-people should not be required to spend more than four hours a day in rooms without windows. The result has been a three-year delay while the architects, Weber, Brand and Partners of Aachen, arranged that the internal partitions between the 6,600 rooms of the largest of all man-made caverns should be replaced by glass (which has, in turn, often been covered by venetian blinds).

- The main contractor for the *Klinikum*, the non-profit organization *Neue Heimat Städtebau*, set up as a cooperative of labour unions in the construction industry, has been involved in a generalized upheaval so widespread it may yet turn out to be the biggest socio-political scandal in the short history of West Germany. (The investigating commission has not yet reported.)

The result is that the *Klinikum*, surrounded by between 5 and 10 square kilometres of still-empty car park, remains unused. But the building is already being

Inside Aachen's great *Klinikum* — but will the patients come?



used for teaching physiotherapists and it is hoped that 80 third-year dental students will arrive in October.

Academics on the Nordrhein-Westfalia payroll half snigger when asked "Why did you let this happen?" "Nothing to do with us", they say, "and anyway the *Klinikum* at Munster also cost a packet". But responsibility does not all lie in Dusseldorf. The university senate was willing enough to take over the city *Klinik*, offering to turn it into a medical school. The architects at Aachen were given not merely an opportunity to build a latter-day cathedral but a chance to try out a theory — the belief that construction and planning could proceed simultaneously.

Some of the immediate consequences are absurd. The new medical faculty is having to teach in the old *Klinik*, now hopelessly run down. And as the day approaches when the hospital may have real patients, perhaps in 1983, the university is alarmed that the *Klinikum's* history (and appearance) will frighten off the patients from whose health insurance policies the operating cost must come.

The *Klinikum* is thus a monument to the economic optimism of the 1960s. Of the three medical centres then planned by the government of Nordrhein-Westfalia for its bemused and then fast-growing university system, that at Munster has been completed and that at Essen abandoned. And nobody knows whether West Germany needs all the physicians now being trained, some 5,000 a year. □

Where the power lies

If there is a power centre in the federal government, with sway over the conduct of science, it must surely be the BMFT. It has a bigger budget than the education ministry, a more personable minister (Dr Andreas von Bülow) and a cleaner brief: spend money and make things happen. BMFT also finances the Max Planck Gesellschaft (see below), the most powerful but the most contentious basic research enterprise in West Germany. The trouble, unfortunately, is that not even the BMFT is as free as it likes to think.

Part of the problem is that the ministry is a tiny organization (and nine of that small number of posts were abolished when last autumn's draft budget was revised in February this year). Taxpayers paying taxes outside West Germany would be alarmed at the prospect of entrusting such small groups of people with such large sums of money. They would also be surprised to learn how civil (in the sense of being open) civil servants become when saddled with the responsibility.

Another part of the problem of telling where the power lies is how that power is distributed. The *Länder* governments have a lot of it. So too do the committees that have been given some kind of constitutional blessing by means of formal agreements between the federal and the *Länder* governments. Although the influence of the *Wissenschaftsrat* has

declined since 1968, its formal recommendations must still be considered.

People also matter. West Germany being the place it is, a speech by some establishment figure, say the president of the DFG or of the Max Planck Society, will carry a great deal of weight. West Germany's preoccupation with the quality of research stems from a public speech by distinguished people who have left the public service and then made their misgivings public.

So science policy is determined in West Germany much as elsewhere, by accretion. The civil servants will defend the existing budget, but will leap at whatever opportunities for innovative expenditure are approved of by the councils of wise men.

Thus the BMFT is the sponsor of West German interests in space, energy, information technology, marine and polar research, while through its sponsorship of the national laboratories (see page 279) it is also directly responsible for much fundamental research, especially in particle and plasma physics. From one year to the next, it is possible to add or subtract relatively small amounts from these large programmes — this year, for example, an extra DM12 million for biotechnology (a 28 per cent increase) and an extra DM40 million for information technology (a 42 per cent increase on last year). More radical changes would be difficult. □

Centres of excellence

THE Max Planck Society (Max-Planck Gesellschaft zur Förderung der Wissenschaften) is internationally the best-known of all West German research organizations. *Everybody* knows *somebody* working at one of the 49 institutes scattered through the country. And that is one of the most frequent complaints about the society: if anything, the "Max Planck" is too successful, providing scientists with opportunities for research far better than those at the universities, for example.

But this is inevitable, given the constitution of the society. Historically, it is the post-war replacement for the Kaiser Wilhelm Gesellschaft, the organization established in 1911 whose Berlin institute provided Einstein with a base in the 1920s. The underlying objective is frankly elitist — to provide distinguished researchers with resources sufficient to support a group of younger colleagues, and to provide all concerned with the security and the equipment necessary for high-quality research.

On many occasions the Max Planck institutes have amply justified their founders' faith. The institute of biophysical chemistry at Göttingen for example, is where Professor Manfred Eigen's use of pulsed lasers pointed the way to novel techniques for following fast

chemical reactions (and won a Nobel prize).

Flexibility is plain. The Göttingen institute has grown to the point at which there are nearly 400 people, many of them visitors from overseas, while the research programme has diversified enormously. This illustrates the Max-Planck contention that once an institute has been established, those in charge are within reason free to follow their changing interests.

Elsewhere, new institutes seem to spring up by mitosis. Thus the clutch of physics institutes at Garching, near Munich, can be traced back to the unique arrangement by which Professor Werner Heisenberg's Institute of Physics was financed in the years immediately after the war. By a succession of fissions, there are now for practical purposes five descendent institutes, one of them the huge plasma physics institute (see page 271) and the others concerned with physics, astrophysics, extra-terrestrial physics (see page 274) and quantum optics.

The Max-Planck Gesellschaft claims also to be vigilant in bringing institutes to an end when they have outlived their usefulness. Again (as with DFG) there is a system of formal invigilation every two or three years, with scientists from elsewhere included among the visiting party. But the list of casualties among

institutes is not long — five have disappeared since 1948, while the thriving coal research institute at Mülheim (in the Ruhr) has become virtually self-financing by means of contract research.

While some Max Planck institutes are from time to time riven by internal disputes deriving from the way in which the direction of the larger institutes is the collective responsibility of senior people — the radioastronomy institute at Bonn seems to have been unlucky in this respect — the most obvious danger is that a group of people who age together will become less sparkling than at the outset of their enterprise. Proof is necessarily hard to come by, although Dr Dieter Raft, general secretary of the Max-Planck Gesellschaft, acknowledges that "we are not satisfied".

Most complaints against the institutes, however, are concerned not with the quality of the work but with the effects of the institutes on other research organizations. By offering security and freedom from teaching to talented younger scientists, does the system unfairly deprive the university system of talent? And should not the institutes be more closely integrated with their local universities? In reality some Max Planck institutes are closely integrated with universities, others are unnecessarily separate (see page 274).

Money to spend

By any criterion, West Germany spends more on research and development than any other state in Western Europe. But the question keeps cropping up, "Are we getting value for money?"

Telling who pays how much for what, however, is complicated by the division of financial responsibility between the *Länder* and federal governments. The *Länder* governments are wholly responsible for the direct support of university research through recurrent budgets, contribute 50 per cent to the costs of DFG and some Max Planck institutes but only 10 per cent to the cost of large research establishments. Industry, of course, is separate.

In 1981, the total spending on research and development is estimated to have been just over DM41,500 million, something like DM750 per head of the population. The absolute amount is greater than that spent on research and development elsewhere in Europe. *Per capita* spending is close on twice the annual spending on research and development in Britain and, with the exclusion of defence research, more than is spent by government and industry in the United States.

Industrially financed research, mostly in industrial laboratories, accounted last year for more than half the total — DM22,490 million. Some officials suspect that this figure may be inflated. Government support for industrial research is estimated at more than DM5,000 million, mostly from the federal government.

There is similar doubt about the contribution of the *Länder* governments to research in universities, this was estimated last year to be DM5,380 million, but this is to some extent to be based on notional divisions of university expenses between teaching and research.

Among the government sources of finance, the federal ministry of research and technology (Bundesministerium für Forschung und Technologie, or BMFT) is dominant. This year (1982) the ministry had DM6,578 million to spend, apparently a real increase over the last year's DM6,073 million. But this year's total includes DM280 million for special programmes of research support in microelectronics, iron and steel and optical communications technology. Thus the funds available for continuing last year's programmes will increase less quickly than inflation.

BMFT is the source of support for most high technology in West Germany. Nuclear energy remains the biggest drain on the budget, with space activities and information technology of growing importance. More significantly, the technology ministry is the channel for the federal government's support of the Max Planck Society.

Centre of confusion

ARGUMENT about the future of the West German Cancer Research Centre at Heidelberg continues. The next landmark in the laboratory's turbulent contemporary history will be the special meeting of the governing body (the *Kuratorium*) arranged for 21 June, when the staff of the laboratory plans to reply to the criticisms of the report by the investigating commission under Sir Michael Stoker, published at the end of March (see *Nature* 8 April, p.481).

Professor Otto Westphal, previously director of the Max-Planck Institute for Immunobiology at Freiburg, and director of the *Krebsforschungszentrum* since March this year, nevertheless hopes senior members of the staff will keep a pact he has made with them that there will be no public discussion of events of the past few years until after the *Kuratorium* meeting.

He does, however, say that the Stoker report was in some ways superficial, and too dismissive of the political nature of the problems that have plagued the centre. Referring to the resignation of his predecessor, Dr Hans Neurath, last summer, he says that it is now plain that there were faults on both sides — Neurath looked for too much change too soon, but was not adequately backed by government officials.

The cancer research centre has willynilly been caught up with politics because both the federal and the *Länder* governments have looked to it for advice on questions raised in the *Bundestag* and elsewhere on the incidence of cancer in West Germany. In the absence of formal channels for these consultations, differences of scientific opinion at the laboratory have been magnified into political differences — a circumstance further complicated by the election of a Christian Democrat government in Baden-Württemberg.

Westphal says that the effectiveness of the cancer research centre has hitherto also been impaired by a poor working relationship with the university clinic, part of which is in the next concrete and glass block. He says that there is already a more constructive relationship between the two establishments, partly because of the openness of some of those recently appointed to the university's medical faculty.

On the centre's role in medical research, Westphal says that West Germany is surely big enough to support a centre able to understand and acquire skills in new methods of treating various forms of cancer elsewhere in the world. Thus, he says, the complaint that the laboratory is not a centre of excellence across the board does not mean that it should be scrapped. In any case, its recent record is far from discreditable, particularly the work on new chemotherapeutic schedules and methods of analysis for the detection of small doses of carcinogens.

Perhaps the laboratory's most valid boast is the use of advanced image pro-

cessing techniques for the accurate three-dimensional mapping of tumours (using some form of tomography), followed by the design of radiation sources (based on a specific implant of radioisotopes) which are optimized to destroy, say, a brain tumour but not surrounding tissue. The centre has the resources to deal with three such cases a week but depends on Heidelberg's neurosurgeons for implantation.

The somewhat down-to-earth character of those achievements is entirely consistent with the original concept of the institute by Professor K.H. Bauer, himself a Heidelberg surgeon and a personal friend of the first West German Chancellor, Konrad Adenauer. The hope in the 1950s was that applied research could help with the treatment of cancer. At first constituted as a foundation (*Stiftung*), the *Krebsforschungszentrum* became one of the research centres supported by the Ministry of Research and Technology as recently as 1976.

The centre's immediate difficulty is shared with the other major research centres dependent on the federal government — staff has to be cut across the board by 7.5 per cent in the next five years. If it is eventually decided that the pattern of the centre's work should be radically changed, the specificity with which the proposed cuts have been defined (so many scientific posts, so many cleaners) and the fact that half of the centre's original research groups are still in being will be a hindrance.

Westphal's own future is unclear. He relishes having brought a measure of calm to the laboratory at which, only a few months ago, one institute director (division head) told his boss at a committee meeting that he would fight him until one or the other went. (In the end, both went, the subordinate after an incriminating letter had been posted to Heidelberg in the wrong envelope.) It is a fair guess that Westphal will be looking for a measure of independence and an assurance of government support.

For the federal government, the problem is more serious. The *Krebsforschungszentrum* fits awkwardly in the clutch of major research laboratories financed principally by the Ministry of Research and Technology. (Its closest relative is the biotechnology laboratory at Braunschweig, west of Hannover.) In reality, however, the existing federal grant-making agencies are conspicuously unsuccessful at supporting clinical research — some say because physicians are so busy making money. With an election two years or less away, will the federal government have the stomach for the long process of consultation, with the *Länder* and everybody else in sight, that might eventually lead to an effective medical research organization? □

Particle physics goes ahead

BEFORE the Second World War, German electron physics and technology was already strong. And despite the flight of physicists from the Nazis, it remained strong afterwards, partly through the influence of the "father of quantum mechanics" Werner Heisenberg and his colleague Heinz Maier-Leibnitz. The tradition has been maintained in one place in particular: the Deutsches Elektronen-Synchrotron in Hamburg.

DESY, as it is called, has become the only national high-energy physics laboratory in Europe which is unquestionably of world class. So much so, that a couple of years ago there was a distinct possibility that DESY would upstage CERN, the big joint European high energy laboratory near Geneva, and go ahead independently to build the next big machine for Europe (the 27-km circumference large electron-positron collider, LEP).

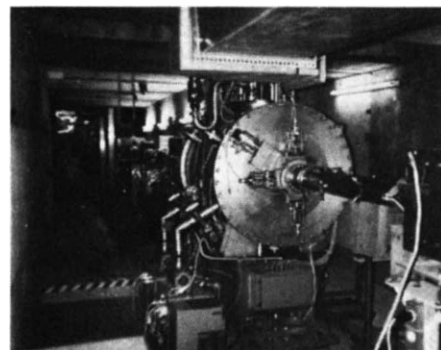
How has DESY managed to become so strong? The laboratory owes much to the canniness of DESY directors in raising money within Germany; and also to good, cost-cutting design of accelerators, rather in the legendary style of Fermilab's Bob Wilson in America. It is not exactly the spirit of Göttingen again: more like

German technology and good management. Also it has been luck. DESY is an electron laboratory, and electron physics has come to the front of the stage, as the electron is now seen to be elementary, in contrast to the other commonly accelerated particle, the proton, which contains three quarks. DESY got into the excitement of charm, and the *Land* of Hamburg (which contributes 10 per cent of DESY's budget) and the federal government in Bonn now look on the place as a little German jewel. The previous director, Professor Herwig Schopper, whose political lobbying in Bonn and Hamburg was so effective, is now director-general of CERN, but his successor, Professor Volker Soergel, although a more private and very different man, has taken over all of Schopper's tactics — in particular, internationalism.

Soergel has attracted the largest American high energy physics experiment ever to be undertaken in Europe: \$4 million of equipment and 30 American physicists will stay at DESY for upwards of three years to make a thorough investigation of the interactions of the bottom quark (the one that came after charm). According to Elliot Bloom, the Stanford University spokesman of the group, there is

"tremendous support" at DESY. Bloom hopes to match and perhaps outgun the only equivalent "bottom" investigation in the world, at the CESR facility at Cornell University, New York.

Bloom will use as the collider DORIS, the electron-positron collider that first put DESY on the map during the charm era of 1974-76; but now it has been completely rebuilt, and should do for the higher mass of "bottom quark" what the old DORIS (and the Stanford machine SPEAR) did for charm.



Superconductivity success at DESY — an accelerator cavity which works on a storage ring.

The other big machine at DESY is PETRA, which shares with PEP at Stanford the accolade of being the highest energy electron-positron collider in the world. However, both PEP and PETRA

become operational in 1984. The German SNS would not be likely to be ready before 1991, even if it got early approval; but then it would produce more than three times as many neutrons (peak flux) as the Rutherford SNS in the first stage, or 25 times as many in the second stage. The corresponding figures for mean intensity are 25 times and 200 times the British SNS — an indication of how sophisticated and complex the German technology would have to be.

On both the British and the German sides the open question is how much collaboration can be established on the two projects. Money for the British SNS is agreed, but a lot more cash is needed for the complex instrumentation (spectrometers and so on) which must accompany a neutron source if it is to be a success. (A major reason for the pre-eminence of the high-flux reactor, the Institut Laue-Langevin at Grenoble, in this field can be traced back to an early and effective emphasis on instrumentation for the institute.) So Britain would be happy if Germany could contribute a few instruments to the SNS. Then, perhaps, if the British economy had improved, there might be some British support for the German machine in the 1990s. Very preliminary discussions are already under way on such matters. But a likely fate for the large-scale German SNS might be that it will not be built at all, unless much wider international collaboration can be set up to support it.

Robert Walgate

More neutrons may cost too much

Is neutron scattering "Big Science"? It is at a price of DM850 million (about £220 million), which is the current tag on a spallation neutron source (SNS) being proposed in West Germany. The idea is to produce a high flux of neutrons, particles which can be used rather like X-rays to analyse the structure and dynamics of many kinds of material, by bombarding a target of uranium with a pulsed beam of protons. Broadly speaking, fluxes much greater than those currently available with "high flux" nuclear reactors can be created in that way, so spallation neutron sources are now seen as the second generation sources in the field, just as synchrotrons have replaced X-ray tubes in X-ray work.

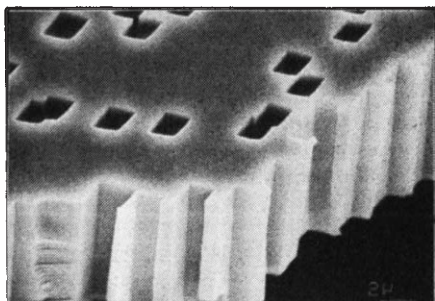
However, spallation sources are not cheap. Only HERA, the electron-proton collider planned by the national high energy physics laboratory DESY (see above), comes close to the SNS in price among major capital projects currently before the ministry of research, and even that is cheaper. But the SNS would provide for a much larger community of scientists than HERA, and it could be built in two half-price stages. Which to buy, HERA or the SNS? Or is there money for both? The decision is due sometime next year.

For the moment, the two interested communities are playing a kind of poker

game. The minister for research and technology, Dr Andreas von Bülow, has asked them to assume that the government would fund both projects, but to stretch the construction schedules of their machines so that the net annual cost would not be too high. However, von Bülow has omitted to say what "too high" would be; so the communities are now competing both against each other and against an uncertain ceiling to pare their costs to the minimum. Nevertheless there is some hope that a recent government commitment to make a major investment in the economy in the middle of next year (at the expense of increased borrowing) may see money being spent on both projects, if only to help the construction industry. This was just how DESY first got the money to build PETRA (see above) some years ago.

The only firm decision so far is that the SNS, if funded, will be built at the Jülich nuclear centre near Cologne, where Professor Hans-Heinrich Stiller is the project leader. (Karlsruhe, an early competitor for the site, has been eliminated.)

The SNS would be bigger (and come on line considerably later) than the only other similar machine in the world, the British SNS under construction at the Rutherford laboratory — which will first



A molecular sieve (see article on GSI, right).

have suffered a trick of physics: the energy region has proved so far to be relatively barren of spectacular results. Nevertheless, PETRA has found evidence for gluons (the photons of the interquark force), and has more recently demonstrated "interference" between the electromagnetic and weak interactions — which indicates the existence of the neutral intermediate vector boson, the present holy grail of particle physics.

Another DESY success (in collaboration with Karlsruhe) was demonstrated only this month: "our little present for LEP", as it is described at DESY. It is a superconducting accelerator cavity, which can reduce the electric power required to drive an electron accelerator by a very large factor (up to tenfold) or, equivalently, raise the energy that the machine can reach for the same power input. Since CERN's likely power bill for LEP is a major headache, the demonstration of working, cheap and reproducible superconducting cavities would be a great step forward. Two weeks ago a single Karlsruhe-DESY cavity successfully drove PETRA to 5 GeV. The cavity has some unique features, and could be produced industrially, but so far it is too expensive: to equip PETRA fully with the devices would cost DM50 million, DESY staff estimate, for a present electricity bill saving of DM2–3 million a year. Nevertheless, savings at LEP would be much greater, and it is clear the design is approaching being practical.

DESY is again looking abroad to raise the finance for HERA, DESY's big (DM600-million) project for the 1990s. (HERA would collide 30 GeV electrons with 820 GeV protons, to probe the lepton-quark interactions. It would use superconducting bending magnets. If for some reason LEP failed, it could be converted to create the intermediate vector boson.) A DESY spokesman said recently that negotiations are already well-advanced if not with governments, with laboratory directors elsewhere, with hope of raising around DM200 million of the cost of HERA abroad. Hamburg has already committed itself to its 10 per cent (DM60 million) which would then leave Bonn with only DM340 million to find — cheaper than the first stage of the spallation neutron source with which HERA might be in competition for Bonn resources (see opposite).

Robert Walgate

An element of risk

THE Gesellschaft für Schwerionenforschung (GSI) at Darmstadt (south of Frankfurt) is riding high. It has one brilliant feather in its cap — the artificial production of element 107, the heaviest so far. And its director, Professor Gisbert zu Putnitz, has ambitious plans for bigger and better experimental equipment.

GSI, the only dedicated heavy-ion laboratory in Europe, lives by its equipment for accelerating heavy ions — even uranium ions — in several stages. At the end of last month, the laboratory inaugurated an extension to its UNILAC accelerator that will double the maximum energy of the ion beams produced to 20 MeV per nucleon. But zu Putnitz is already looking beyond that target.

Element 107, represented by the isotope with 155 neutrons, was made at GSI last year by the collision of accelerated chromium-54 with a target of bismuth-209. As with all experiments of this kind, the chief difficulty is to demonstrate that the intended element has indeed been produced. The team at GSI used a novel arrangement of electric and magnetic fields to demonstrate their few nuclei of element 107 and thus to break the near-monopoly on the creation of heavy elements which the Lawrence Radiation Laboratory in the United States has enjoyed in the past few years.

More intriguing, however, is the demonstration of a novel form of radioactive decay — the emission of protons rather than electrons from nuclei that are deficient in neutrons. By the collision of a beam of nickel-58 ions with a target of ruthenium-96 for example, it has been possible to synthesize the isotope lutetium-151 which has 24 neutrons fewer than the stable isotope of the element. (The isotope thulium-147 is also subject to

proton decay.) Plainly this novel form of nuclear instability has been a great fillip to nuclear physics — and not merely in West Germany.

The laboratory says, however, that it is not merely a nuclear physics establishment but a practical place. By way of evidence, it cites the use of molecular beams for producing molecular sieves. What better than a beam of heavy ions to punch holes of molecular dimensions in a synthetic membrane? So filters are being made for instruments that measure particulates in air and models constructed for studying the permeability of biological membranes.

So what of the future? Professor zu Putnitz clearly regards the present energies at which heavy ions can be produced as only a modest beginning. Ultimately, there will be a need for ions with energies of 500 MeV per nucleon or even 10 GeV per nucleon. Such energies cannot be achieved with a linear accelerator of reasonable cost and size, and GSI has therefore proposed to build two interlinked synchrotrons, presently called SIS 12 and SIS 100. The smaller one, SIS 12, would use UNILAC as an injector and would accelerate ions to about 1 GeV per nucleon. The next synchrotron (SIS 100) would take over from there and further accelerate the beams to the maximum energy of about 10 GeV per nucleon.

Enough land is available for both machines. The cost, just under DM90 million for SIS 12 and just over DM 150 million for SIS 100, is the stumbling block. But SIS is high on the government's list of major projects; zu Putnitz is optimistic. Indeed, if funds are short, he would prefer to start by building SIS 100. Time alone will tell whether he will be able to follow this more imaginative but no doubt risky approach.

Konrad Guettler

Research without responsibility

PROFESSOR Klaus Pinkau, director of the Max Planck Institute for Plasma Physics at Garching-near-Munich, is a square-jawed square-built man with a shock of grey hair and a ruddy complexion who exudes enthusiasm. He thinks he knows something of what is wrong with the state of science in West Germany.

First, he says, people are needlessly depressed by what is in effect an illusion, what he calls the "echo-effect". Everybody must accept that the United States is now the chief source of scientific discovery, and American scientific journals the chief medium for the announcement of new developments. Inevitably, however, this implies that papers by West German scientists are referred to less frequently, and less

fulsomely, than their merit would demand. Worse still, there is a tendency for science journalists and even scientists themselves to take note of some development in West Germany only if it is first applauded, or approved of, in the United States.

In reality, Europe (and West Germany) has more to boast about than anybody acknowledges. Has not the COS B gamma-ray satellite (switched off last month after seven years of operation) been a unique and successful demonstration not merely of the technique but of the capacity to formulate an adventurous project?

So what else is good in West Germany? Pinkau echoes the common response by referring, first of all, to "Eigen's group in Göttingen". But his main impression is that West Germany has done best in those

fields in which there were enough people still active after the Second World War to provide a nucleus of active research. Perhaps nuclear physics, especially the work with heavy ions at Darmstadt (see page 271), is representative of the best.



Professor Klaus Pinkau: "We do second-rate research rather well".

Like others, Pinkau thinks that bureaucracy has had a baleful influence. Why should it have been left to a committee of the *Bundestag* to decide, last December, which six posts at his laboratory should be abolished? But the irritation caused by such happenings is less important than the way in which the bureaucracy's existence undermines the sense of responsibility that professional scientists should enjoy. If everybody knows that, in the last resort, distant committees of officials will make the most detailed decisions, how can working scientists shoulder the responsibility implicit in their promises?

Pinkau shares the common concern about the reform of the universities, but in a novel way. The problem is that the universities have also lost their sense of responsibility. He agrees with the opinion that "we do second-rate research rather well". He is doing what he can, personally and by encouraging his colleagues to follow his example, by teaching regularly at the technical university at Munich.

The lack of responsibility — the freedom to act independently — is here again Pinkau's main worry. "The government", he says, "must realize that by restricting the independence of scientists, they are killing science". He acknowledges that the Max Planck Society has an enviable reputation for not being bureaucratic, although his own institute is in the significantly different position of being financed directly from Bonn.

But even with this proviso, Pinkau answers a firm "yes" to the question "Should the Max Planck institutes be merged with their neighbouring universities?". That would be good for research, but in any case there is too much tension between university and Max Planck scientists for comfort. □

New ways with fusion

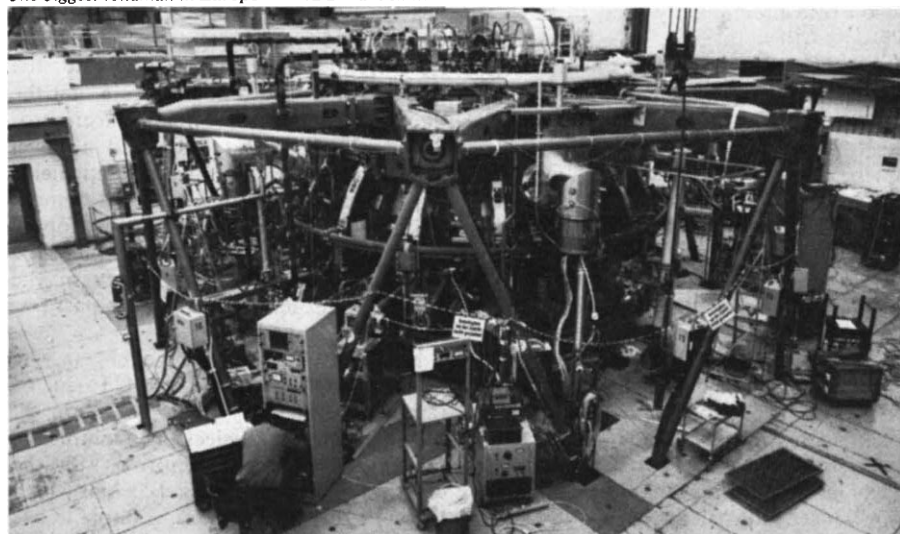
In 1978 the European decision to build the Joint European Torus (JET) at Culham in the United Kingdom rather than at Garching in West Germany seemed a blow to the German plasma physics community. For JET is the principal experimental facility in the Euratom plasma physics programme, and for when national programmes have to compete for funds with collaborative international experiments whose funds are necessarily committed in advance, there is always a danger that they will be squeezed.

The main plasma physics research laboratory in West Germany, the Max-Planck-Institut für Plasmaphysik (IPP) at Garching near Munich nonetheless continues to run a thriving national programme. But the generally less favourable

economic climate of the past few years has taken its toll; an initial multitude of experiments has gradually been reduced to two main lines of research. One of these is centred around ASDEX, the biggest tokamak machine in Europe, which was commissioned in 1980 and has already yielded important scientific results.

What excites the people at Garching about ASDEX are the diverter coils which produce a magnetic field allowing for control of the level of plasma impurities. The stability and lifetime of any contained plasma is severely limited by the impurities introduced through interactions between the plasma and the wall of the container. The diverter chambers of ASDEX significantly reduce the level of metallic impurities and lighter species such as

The biggest tokamak in Europe — ASDEX at Munich



Jülich's jewel

"COME and see our jewel", said the man behind the wheel, pulling up outside a hanger. The jewel in question is the fusion experiment called TEXTOR, a machine recognizable as what it is from its toroidal shape but with the advantage that it can be separated into two halves so that the interior can be rebuilt.

TEXTOR, partly financed by the European Community as part of the joint programme of thermonuclear experiments, has so far cost DM110 million, with close on DM50 million still to go. With its discreet constructor's label, Krupp, the machine is as nicely engineered as it could be.

The torus is intended for the study of problems that may crop up in thermonuclear reactors thirty years from now. It is a small tokamak designed to examine the interaction between a hot plasma and the containing walls, the behaviour of wall materials under neutron irradiation and the processing of tritium, the

necessarily radioactive component of likely thermonuclear fuel. Everybody is delighted with the way it works.

For a nuclear research centre such as the Kernforschungsanlage Jülich, set up in 1956 by the government of Nordrhein-Westfalen but since 1970 supported to the tune of 90 per cent by the federal government, a long-term project such as this must be a comfort.

The establishment is best known for its development of a high-temperature reactor, an experimental version of which went into operation in 1967, producing 46 MW of heat. The prototype of that design being built at Hamm-Uentrop nearby will function only in 1985 (seven years late), producing 300 MW of electricity.

The technical problems are those of making reactor components that will operate reliably at 950°C for years on end, but the costs are also high. So Jülich is pushing hard a scheme for long-distance energy transmission in which fast reactors would convert methane (and water) into hydrogen and carbon dioxide for reconversion at some distant point.

oxygen. The mechanical devices used elsewhere in tokamak machines are said to be comparatively ineffective.

The second objective of ASDEX is to study the properties of plasmas heated by beams of neutral atoms. The original neutral beam injectors are being upgraded to a total power of 2.5 MW which should lead to an increase in plasma temperature from 6×10^6 K to 2×10^7 K. There are plans to use radio-frequency heating to increase plasma temperatures still further, and to use a deuterium pellet injection system to replenish the plasma particles removed by the diverters.

The ASDEX device will remain the major focus of research for several years, but plans for an upgraded version are already being drawn up with support (in the design phase) from the European fusion programme. As well as being a bigger machine, the distinguishing feature of the version being planned is that the diverter coils will be external to the main toroidal field coils, an arrangement considered to be essential for a fusion reactor.

Most of the research at ASDEX is of direct relevance to JET (also a tokamak machine) and the laboratory says that there are close links between the two establishments. But IPP has not put all its eggs into one basket; it continues its research into the physics of stellarator machines. In the present machine (called Wendelstein VII-A) the peculiar stellarator magnetic field configuration is achieved by a set of toroidal field coils surrounding the inner helical coils. But the laboratory is planning an Advanced Stellarator in which these two sets of coils would be replaced by one, each of them with a somewhat different twisted geometry. The result is expected to be improved plasma stability at a higher plasma pressure. The design phase has begun and the new machine could be working as soon as 1985.

Although the Garching institute is technically part of the Max-Planck-Gesellschaft, its size and large annual (running) budget of DM110 million made it a natural candidate for membership of the association of the large science centres, AGF. The institute's finances are outside the usual Max Planck pattern — a quarter of the budget is derived from Euratom, with the remainder split 90:10 between the federal government and the *Land* of Bavaria.

Not surprisingly, other Max Planck institutes are uneasy at the presence of such a cuckoo in their nest. Fusion research is, however, one of the few European programmes that really work, and it is difficult to imagine how such a successful research centre could be effective on a much smaller scale. Nevertheless, as the size of fusion reactor experiments becomes even larger in the future, it is likely that one of the more applied research centres, such as the huge *Kernforschungszentrum* at Karlsruhe may take a bigger share of the development — its contribution to research

Alternative routes to fusion

THERE are other means of inertial confinement fusion which have received considerable attention and funding elsewhere: laser fusion and heavy-ion beam fusion. The main difficulty with the former is the high power output required by the lasers and reliable operation with a high pulse repetition rate. Heavy-ion beam fusion research suffers from the handicap of requiring a very large initial investment in the ion beam accelerator. Some of the relevant ion beam studies are being carried out at the GSI accelerator (see below) near Darmstadt but with low priority. A high-power laser project group originally formed part of IPP at Garching but some time ago it was

expanded and elevated to the status of the separate Max-Planck-Institut für Quantenoptik. Although still sharing a site with IPP at Garching, the research emphasis of the new institute is divided between laser fusion, laser spectroscopy and laser chemistry. Its fusion research is carried out with a high-power iodide laser and is aimed at understanding the fundamental aspects of energy transport within the compressed fusion pellet. The emphasis on some restricted topics of research appears to be deliberate, although some foreign concern seems to have been expressed about a much more expanded national laser programme.

Konrad Guettler

at Garching takes the form of technological development of such items as the pellet injection system.

Within the national German fusion programme, the Karlsruhe centre tends to be most active in magnetic field technology and materials study, but the centre is also involved in system design studies. In particular, it maintains a modest presence in two lines of fusion research: inertial confinement fusion using light ion beams and fusion by magnetic confinement in a tandem mirror machine. The light ion fusion studies involve a pulsed high-power ion generator, whereas the tandem mirror configuration is only at the system design stage. Earlier mirror experiments at Lawrence Livermore National Laboratory in California yielded promising results, yet the research at Karlsruhe seems to be the only investigation of its kind in Europe.

Fusion research in West Germany seems thus to have retained an enviable diversity,

the commitment to JET notwithstanding. The machines now operating, at IPP and elsewhere, are producing a substantial harvest of data. And with funds secure for the initial upgrading of the major facilities, the institute has a viable programme for the 1980s. Its involvement in the study groups for the Next European Torus (NET) and the international INTOR project should leave it well placed in any competition for a future international facility.

Yet the time scale for break-even fusion power seems to be receding further and further; Klaus Pinkau, director of IPP, is quite frank in saying that two or three steps will be necessary after operating experience with JET, perhaps by the end of this decade. Each step seems to require ten years or so, so that it may not be known until the year 2020 whether fusion is technically and economically feasible. "I'll be dead by then", he says.

Konrad Guettler

An astrophysics star is rising

WEST GERMAN astronomy and astrophysics are neatly parcelled up on wavelength lines: the Max-Planck-Institut für Radioastronomie in Bonn (see next page) looks after the radio-wavelength part of the spectrum, the Max-Planck-Institut für Astronomie in Heidelberg looks after the optical region and the Max-Planck-Institut für Physik und Astrophysik (with its Institut für Extraterrestrische Physik) in Munich deals mainly with the short wavelength domains of UV, gamma-ray and X-ray astronomy. The Munich institute is the major West German institute involved in satellite-based experiments and has an ambitious programme for the 1980s.

The gamma-ray part of the package is perhaps the most distinctive. Balloon-borne telescopes are used for low energy studies, while the high-energy domain has been studied as part of a European collaboration using the COS-B satellite, shut down only in April this year after more

than six years of operation. The users are delighted with the way this instrument has performed but also with its conception. "It shows", Professor Joachim Trümper, head of the institute, says, "that European scientists can still be the first with a good idea".

Even so, the prospects for further research in the field now depend on plans for the Gamma-Ray Observatory (GRO) satellite of the US National Aeronautics and Space Administration (NASA) for which the institute is helping to design one of the telescopes. Its other gamma-ray investigations centre mainly around the Solar Maximum Mission and the ISEE-3 satellites, which are specially equipped to study solar flares and gamma-ray bursts.

The magnetosphere and the interplanetary medium constitute the second major focus of the institute's programme. The Earth's magnetosphere is being

investigated with experiments aboard the European GEOS-2 satellite, and the interactions between the magnetosphere and the solar wind with the ISEE-1 and ISEE-2 satellites respectively. While the analysis of the data from these satellites will keep people busy for many years, what excites them most are the preparations for the next mission — a major joint project between NASA and European institutes called the Active Magnetospheric Particle Tracer Experiment (AMPTe). It consists of three major components. The Munich institute is building an Ion Release Module, NASA is responsible for the Charge Composition Explorer satellite and the British Science and Engineering Research Council is contributing a subsatellite equipped for *in situ* plasma diagnostics. The release module will inject artificial plasma clouds into the solar wind and the tail of the magnetosphere, and the two other satellites will measure the interactions between the cloud and the ambient plasma.

For the future, the X-ray astronomy group seems to have even more dazzling prospects. Apart from its own balloon experiments, the institute is a major participant in the EXOSAT satellite soon to be launched by the European Space Agency. But its most ambitious project is ROSAT, a large X-ray observatory designed for launch by the space shuttle in 1986 or 1987. This instrument has been designed to have much better angular and spectral resolution than even the NASA Einstein Observatory which ceased functioning last year.

Primarily a national project, this satellite should give West German scientists a commanding place in X-ray astronomy at the end of the decade. The initial observational programme is a sky survey for the first half-year after launch which should reveal many more X-ray sources, given that the satellite's sensitivity is three times greater than that of the Einstein Observatory. This survey is to be followed by a one-year study of interesting sources. If all goes well, the satellite could even be retrieved after a couple of years by the space shuttle and refurbished.

Although a national project, ROSAT will provide observation time for other astronomers. Negotiations are under way with NASA for a US instrumental contribution in exchange for time, while there is to be an extreme-UV telescope built by a consortium of British universities.

So in the late 1980s the focus of attention in the field will shift from America to Europe. Repeated cuts in the US research budgets have put the competing Advanced X-ray Astronomy Facility further back, even though it has received the highest priority in the recent Field report (see *Nature* 8 April, p.482). And with no successors in sight for the UK Ariel satellites, ROSAT will be the only source of X-ray data for years to come.

Konrad Guettler

Contrasts in Max-Planck styles

MAX PLANCK INSTITUTES seem to come in all kinds of shapes and sizes. The largest and most costly of them is the institute for plasma physics at Garching, but the radioastronomy institute at Bonn is similar in that it owes its existence to equipment so expensive and distinctive that it cannot easily be the property of a single university department. The institute's boast is a 100-metre high-frequency radiotelescope.

At the other end of the Max Planck spectrum is the newly created (1980) Institute of Mathematics, which is closely a part of the University of Bonn and which has the further distinctions that its personnel consist largely of visiting mathematics professors (with graduate students from the university) and that it is the first example so far of a Max Planck institute created from one of Deutsche Forschungsgemeinschaft's special research programmes (*Sondersforschungsbereichen*, see page 266). Although the institute will not become a charge on the Max-Planck-Gesellschaft until 1985, it already has a shiny new name-plate on its handsomely constructed building.

Technically, the radioastronomy institute is inevitably the more spectacular. The 100-metre dish sits in a well-wooded valley at Effelsberg, 30 kilometres east of Bonn. It has been designed to operate at frequencies up to 50 GHz (a wavelength of 6 mm) and beam width at 1.2 cm is reckoned to be 35 seconds of arc.

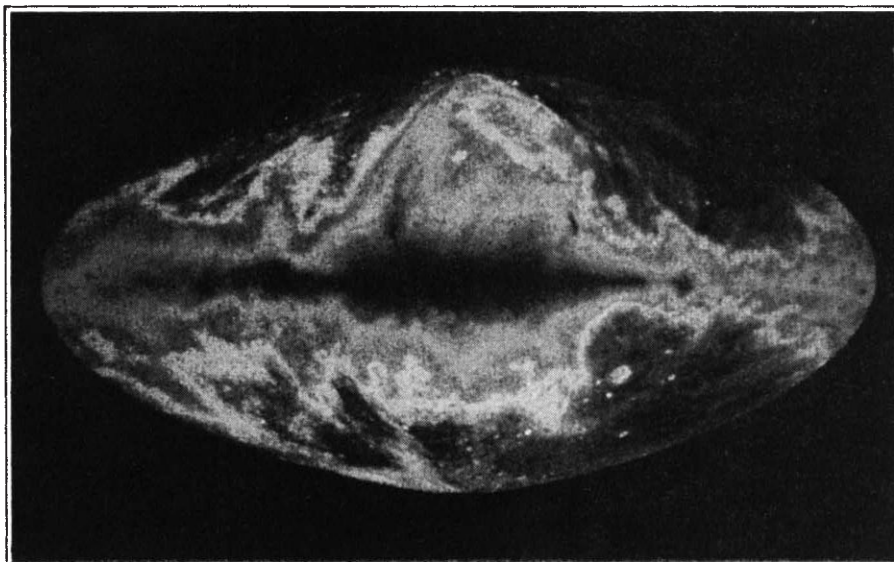
The total cost of the dish (completed in 1972) and the ancillary equipment was DM 40 million, a substantial part of Max-Planck-Gesellschaft's capital budget more than a decade ago. The staff (including a score or so of visitors) amounts to more than 180 people, of whom a third are

scientists. The institute is divided between an office in Bonn and the field station at Effelsberg, and includes a substantial technical effort at both places on the design and construction of detectors for use with the telescope.

Operationally, the telescope has been an immense success, at least in part because of the cleverness with which the structure was designed. The objective is somehow to preserve the parabolic shape of the 100-metre dish whatever the elevation. This has been accomplished in the Krupp-MAN built instrument at Effelsberg by attaching a huge counterweight by a network of struts to the back of the dish so that the dish can distort only into another parabola. The result is a dish that is substantially lighter than rigid construction would have required.

The staff at the mathematics institute is by comparison inconspicuous. The director, Professor Friedrich Hirzebruch, says that he and his two senior colleagues from the mathematics department at Bonn remain on the university's payroll, but that he is relieved of administrative duties (but not teaching) on account of the time spent at the institute. He thinks he may apply to Max-Planck-Gesellschaft for two permanent positions for mathematicians, but the bulk of the budget, roughly DM 2.5 million a year, will still be used to support mathematicians visiting from elsewhere in West Germany and abroad.

In Hirzebruch's view, an institute of mathematics is necessarily a place for peripatetic people. Since his group was formed in 1969, he says that it has acquired an international reputation comparable with, say, those of the groups at the Princeton Institute of Advanced Study, the



A map of radio-sky intensity at 408 MHz compiled at the Max Planck radioastronomy institute at Bonn from data gathered over a period of 15 years at Bonn, Jodrell Bank and Parkes (Australia). Data reduction was by means of a Cyber 172 computer at Bonn. Prominent patches along the mid-line of the sky are the local arm complexes Cygnus X (left) and Vela X (right).

Institut des Hautes Études near Paris and the University of Warwick as being places where mathematicians can work on interesting problems with interesting colleagues without having permanently to tear up their roots at the place whence they came. But Hirzebruch also sees his peripatetic working group as a direct benefit to the mathematicians at Bonn.

The links between the institute of radioastronomy and the local university seem much less immediately productive. Professor Richard Wielebinski, the Polish-born Australian immigrant who is now one of the laboratory's two directors (the executive director is Professor Peter G. Metzger) says that the radioastronomy institute is, above all, a national research centre. A substantial part (more than 20 per cent) of the 100-metre telescope's time in the past two or three years has been used for coordinated interferometric observations in which radiotelescopes as far apart as California (Goldstone) in the West and the Soviet Union (Crimea) in the East have been used to produce the intensity of radio emission from distant objects such as the radio galaxy 3C298 with a resolution of 0.5 seconds of arc.

Long baseline operations such as these require long-term planning and the blocking-out in a somewhat arbitrary fashion of other opportunities for observation. Even so, the institute is planning to extend its international operations. The institute is the vehicle for the Max-Planck-Gesellschaft funds being channelled into the construction of a 30-metre radiotelescope being built in Spain to operate at frequencies of 80 GHz and above. This will be for a time, when tested in operation next year, the largest instrument of its kind in this region of the spectrum. The instrument will be used for observations of extragalactic carbon monoxide and continuum radio emission (the latter being one of Wielebinski's particular interests). It is also intended that the Spanish instrument should be used in conjunction with an array of three 15-metre dishes being built near Grenoble in France under a fifty-fifty agreement between Max-Planck-Gesellschaft and Centre National de la Recherche Scientifique, but that agreement has been made at headquarters level.

Off its own bat (but with approval from Munich), the institute has made a fifty-fifty deal with the University of Arizona that will lead to the design and construction of a 10-metre sub-millimetre telescope, to be built in Arizona. That agreement is to be signed in June this year.

What these two institutes therefore have most conspicuously in common (from 1985, in the case of the mathematics institute) is that the money comes from Munich. There is also a sense in which a direct comparison between them is unfair. One (the mathematics institute) is a device for channelling support for old-fashioned scholarship through a talented scholar to a

university which, even though founded in 1818 in the aftermath of the Napoleonic wars, is distinguished in this and other fields. The other, the radioastronomy institute, is either a national research centre, intended to put West German radioastronomy on the map, or a national research facility, to be used by whichever West German astronomer has a sensible idea as to how the equipment should be used.

The trouble seems to be that this Max Planck institute pretends to be neither of those things but rather, in the Max Planck rhetoric, to be a free-living community of independent scholars which, nevertheless, by means of its senior people's honorary professorships (at the local university), its downtown location so close to the Department of Astronomy at the University of Bonn that the two institutions can share a library and its willingness to take in graduate students from everywhere, is intrinsically part of the university system. The irony is that the university's department of astronomy seems likely to succeed in its application to Deutsche Forschungsgemeinschaft for the funds with which to build another radiotelescope at a different site.

What follows is a strictly personal impression. First, the two institutes have distinctly different roles. The mathematics institute is not merely a source of scholarship but a way of enlivening mathematics at the University of Bonn, while the institute of radioastronomy, in spite of its links with university astronomers in West Germany and elsewhere, must be judged primarily by its



Effelsberg's 100-m dish: productive but an ivory tower?

own staff's output of research results. To some extent, of course, these differences are explained by the differences between the subjects — mathematicians are mobile, radioastronomers to some extent tied to their instruments. But there are other ways of organizing the use of large research facilities, with the American pattern of open access through user committees at one extreme and the British tendency to base radiotelescopes in university departments at the other. More concessions at Effelsberg in one direction or the other could not fail to embed the use being made of this splendid instrument more firmly in the scientific community's consciousness.

Making a business of research

By what trick can a group of only four tenured academics run a department with 400 students, 160 of them doctoral students, spend the best part of DM20 million a year and yet keep the department's well established reputation for being the best academic institution of its kind anywhere in the world? The department is the machine tool institute at Aachen, one of the fourteen specialized institutes in the mechanical engineering complex at the Rheinisch-Westfälische Technische Hochschule (RWTH). The trick is to run the department as if it were a business.

The four tenured academics are university professors. Their formal duties are to lecture to the undergraduates, but each also has under his wing a small clutch of research groups, perhaps three or four. The research groups are run by senior engineers, hand-picked from among those gaining a doctorate in the department and employed as the need arises on short-term contracts.

Of the total cost of the department, no

less than eighty per cent comes from outside RWTH, principally from the federal government and its grant-making agencies. The brunt of the research work falls on the graduate students, paid out of project grants, but the department also makes a special point of engaging undergraduates part-time in its research work (and pays them for their trouble). Ten per cent of the successful diploma candidates are kept on for doctoral work, on which they spend between five and eight years (the average is about six). Once their dissertations are completed, they must find a job elsewhere.

That step appears to present very little difficulty. Apart from the institute's high reputation, the Laboratorium für Werkzeugmaschinen und Betriebslehre prides itself on having the closest possible relations with companies in the metal-forming industries of West Germany, many of which play a crucial part in helping to define the department's research programme. But the department will add a project to its portfolio (and apply to some

Hard management and software

THE machine tool institute's reputation stems directly from the single-mindedness of its founder, Professor Adolf Wallichs, who in 1906 seems to have taken fright at developments in production engineering in the United States and to have embarked on a research programme in a small cellar. One of his achievements was to persuade German industries to contribute to the cost of a building and the equipment to go with it at the height of the post-war inflation in 1924.

Wallichs was succeeded in 1938 by Professor Herwat Opitz, whose 37-year spell in office saw radical developments in, for example, the design of gear-cutting tools and, after the Second World War, the threefold growth of the institute. Since 1973, the management of the institute has been shared between the occupants of the three full university chairs (*Lehrstühlen*) among whom the chairmanship of the department rotates. (Metrology is for the time being the poor relation.)

The research programme is now dominated by the application of computers to production processes. Thus the design section is up to its eyes in

computer-aided design (CAD). Here and elsewhere, part of the objective is to produce a library of software that can be used by the small to medium sized manufacturers that dominate this sector of West German industry in the optimization of, say, a gear train — and the automatic draughting of the drawings needed. Similarly, using banks of data built up over the years on the characteristics of various cutting and metal-forming processes, computer programs are being designed so as to identify the best way of producing metal parts of various forms.

The search for accuracy and reproducibility is a recurrent theme in the research programme, whence the current interest in real-time measuring techniques. Similarly, computer techniques are being used in the analysis of how machine tool structures are deformed by stresses arising during use.

While all this software is accessible to would-be industrial users, specialized seminars (at Aachen but also at Zurich) are regarded as essential means of propagating the new ideas that arise, as are the biennial international conferences on machine tools, the last of which last year attracted 2,000 participants.

such organization as the Deutsche Forschungsgemeinschaft for funds) only if the outcome of its work can be published in the open literature. Consultancy on specific problems for industrial companies is only a modest part of the department's work.

This unique way of doing academic business has, in effect, made the institute both the research laboratory and the source of skilled engineers for much of an important sector of West German industry. Yet this is one of the smaller of the fourteen institutes catering for the 5,300 mechanical engineering undergraduates now registered at Aachen.

But is this not a narrow way of training engineers? Yes and no is the customary answer. For the first two years of their academic careers, students follow a more or less common course, heavy on mathematics and physics or chemistry as the intended speciality may suggest. On paper, the undergraduate course should take four years, or eight semesters, divided into the two equal halves of *Grundstudium* and *Hauptstudium*. In reality, par for the course is more like six years, although a small percentage of students win their diplomas after 4½ years. Along the way, some 30 per cent of Aachen's engineering students fail to jump one hurdle or another, although it is reckoned that only seven per cent of them fail to complete some kind of first-degree course, perhaps after moving to some other university. Hothouses like the machine tool institute are responsible only for the second half of

an engineer's education.

The rigours of Aachen's engineering courses seem not to have deterred school-leavers from signing on. Indeed, business is booming. This year's intake in engineering is up on 1980–81 by between 10 and 20 per cent, according to the field, while the volume of enquiries suggests that there will be a further jump next October. The proportion of women remains negligible.

The apparently steady increase of the length of time needed to win the right to the title *Dipl.-Ing.* is nevertheless a source of some concern. There is an unavoidable conflict between the need to give graduates some marketable breadth in their fields and

the objective, still held to, that graduates should know about everything there is to know.

The decline in the knowledge of entering students of mathematics and basic science has also made it necessary for RWTH to provide extra courses in mathematics in the September before the first year begins. Apparently what has happened is that students seeking high marks in the school-leaving *Abitur* are opting out of the extra three hours of mathematics offered each week in the last two *Gymnasium* years.

In this respect, RWTH makes more concessions to its students' needs than many other West German universities, where students are usually left largely to their own devices. Legally, however, it has no control over the quality or even the numbers of those who elect to join engineering courses. The *Abitur* gives anybody the right to sign on for what he chooses, and that is that.

Nor, for the time being, does RWTH appear to have much interest in leavening the education of its engineers with a dash of the humanities (along the lines of the 20 per cent of time students at Massachusetts Institute of Technology are required to spend following courses in the humanities). As it happens, RWTH almost accidentally acquired a philosophy faculty in the heyday 1960s (together with a teachers' training college), and the senate will soon have to decide whether to respond to the financial crisis in Nordrhein-Westfalen by taking the knife to that cuckoo in the nest. The news that the Electrotechnische Institut in Zurich, with which Aachen has close links, is making a few experiments of this kind has unsettled hard-liners.

RWTH seems also to have been comparatively untouched by the wave of recent university reform. In 1968, it was slow to follow other West German *Technischen Hochschulen* in calling itself a university. On reflection, people are glad that they have kept the name first coined in 1870. And while there are student representatives on most committees, their proportions are such that they can be voted down when necessary. □

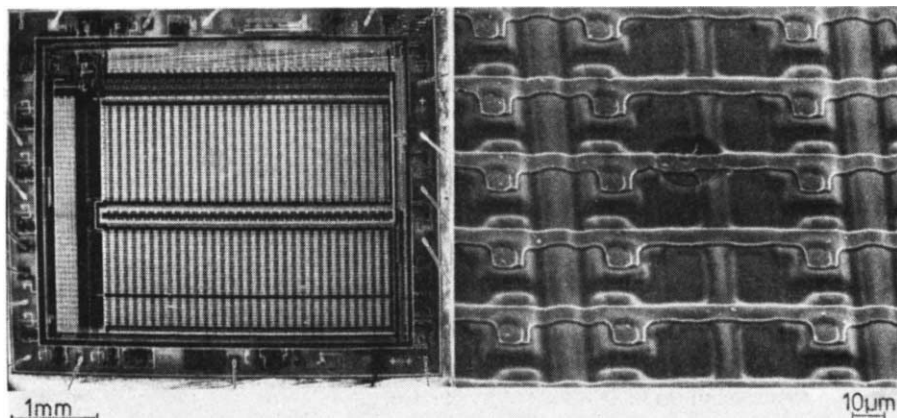
Where graduates make good

SIEMENS AG, the largest employer of scientific manpower in West Germany, is not so much a source of monthly pay cheques as a way of life. The company offers those who work for it attractive fringe benefits such as pensions, while it makes a point of recruiting all its senior managers from within its own ranks. Indeed, the company boasts that the members of its board of directors are almost all technical people who have worked their way up within the hierarchy — and that there are no lawyers, only money people, from outside. The result of all this is that recruits to Siemens who survive the first five years are likely to stay in what has

become a remarkable example of a technical enterprise run by scientists and engineers.

So how does Siemens recruit its technical people? Of the 180,000 employees in Germany, more than 26,000 are technically qualified. In recent years, to make good losses and to sustain a growth of 2.5 per cent a year, the company has been recruiting about 2,000 graduates from the universities and the *Fachhochschulen*. What with the recession, this year's intake will be no more than 800, however.

In the German university tradition that students must fend for themselves, university careers offices do not exist. So a re-



Technique for non-destructive testing of microcircuits developed by Dr H. Rehme at Siemens-Perlach. Left-hand panel represents secondary electron emission by an electron probe scanned over the surface. Dark areas are at positive voltage. The dark line across the lower half indicates the presence of a defect affecting a whole row of circuit elements and revealed in the electron micrograph (right-hand panel).

cruiting team from Siemens trudges round 20 universities and 60 *Fachhochschulen* twice each academic year. On balance, the company prefers to recruit engineers after the first degree (*Diploma*), simply on the grounds that it is easier to take on people in their twenties (the median age of university graduates in engineering is between 26 and 28) than in their thirties.

With the experience gathered since Werner von Siemens founded the company in the nineteenth century, the recruiting men now know where to go. Of the university recruits, 47 per cent are electrical engineers. Physicists make up 13.5 per cent of the university recruits, while the past few years have naturally seen a rapid growth of the recruitment of mathematicians and information scientists. Briefly, the company has a well-trodden selective path between the good engineering schools in West Germany, but also, interestingly, in Austria. Something like 10 per cent of its skilled labour force is from outside West Germany.

So how well is Siemens satisfied by the performance of the country's engineering schools? The specialization which is now common in the bigger and better schools is in some ways an embarrassment. The University of Karlsruhe, for example, produces graduates in electrical engineering under twenty different labels. Siemens approves of the objective — that a qualified engineer should know all there is to know in his or her chosen field — but wishes that it were possible also to help young engineers to be more flexible.

The consequences of the successive reforms of higher education are not welcomed. Siemens people shake their heads over the plight of some of the new universities such as Bremen, which have buildings and teaching staffs but which have failed to attract students of high quality in the numbers originally planned. They also agree with the widespread criticism of the decision that graduates of both the *Technische Hochschulen* and the *Fachhochschulen* should in future append to their names indistinguishable degrees — *Dipl. Ing.* for all. The result, they say, is that potential employers will not be able to rely

on the uniformity of standards hitherto ensured by the various boards of engineering operating nationwide.

The company's chief concern, however, is that the attitudes of young people leaving engineering schools in recent years have been sharply different from those in the more distant past. People have been less competitive than they used to be, less eager to get on. They have also been corrupted by concern about the environment, a distaste for affluence and all that. But, so the argument goes, in the past year or so there has been a change. People are beginning to respond to the challenge presented by Japan. It's vital, said one company official, not just for West Germany but for the whole of the West that the Japanese should be challenged effectively at their own game of innovation.

The most striking feature of the company's use of its technical people is that close on 10,000 of its qualified staff work in research and development in laboratories scattered through the company's six operating groups but also in two central laboratories, one at Munich and one at Erlangen (not far away). The central laboratories are thus an important part of the cement that holds the six operating divisions together.

The scale of Siemens's investment in research and development should be sufficient to give it a sporting chance. For the company as a whole, 48 per cent of sales in 1979–80 consisted of products developed in the previous five years. Inevitably, the contributions of recently developed products are even higher in the company divisions responsible for components and information systems. Research and development cost more than DM3 million a year, exceeding 9 per cent of the company's sales (56 per cent of which are outside West Germany).

The central laboratory at Munich is housed in a complex of Lego-like buildings on the edge of the housing desert of the suburb of Perlach. Its managers say that they encourage proposals for research projects from members of the laboratory staff, and although most projects are oriented towards products that may ulti-

No moving parts

ONE of the first instruments whose operation depends on the special theory of relativity is a spectacularly neat gyroscope built at the Siemens research laboratory at Munich-Perlach. Briefly, the device is a circular coil of single-mode glass-fibre around which radiation beams from a single semiconductor laser diode are sent in opposite directions. Rotation of the coil about its axis changes the velocities of the two opposing light beams, and thus the position of the interference fringes produced by recombining them.

The prototype instrument, built by Gerhard Schiffner (now at the University of Bochum), Benhardt Nottbeck and G. Schöner, consists of 2.88 kilometres of optical fibre wound on a 12.3 cm diameter former. To obtain an analogue signal proportional to the rate of angular rotation of the coil, the phase of the counter-travelling light beams is modulated by means of a short length of fibre whose length is modulated by means of a piezoelectric element. The signal produced by the recombined beams at a silicon photodiode is amplified and analysed by means of two lock-in amplifiers, one at the modulation frequency and one at twice that frequency. The ratio of the two signals can in principle provide a measure of rotation rate independent of power output or of the attenuation of the glass fibre.

The obvious rotation rate to measure is that of the Earth — some 10 degrees per hour for an axis pointing north-south at the latitude of Munich. Measurements of this rate suggest that the sensitivity of the prototype instrument is limited by noise to about 0.3 degrees per hour, while drift of the calibration scale may be about 0.5 degrees per hour. Temperature fluctuations (affecting the length of the optical fibre and its optical properties) and even fluctuations of the Earth's magnetic field may contribute to drift.

Siemens has little to say about the potential applications of the instrument, but the attractions of what may be a sensitive gyroscope with no moving parts are obvious. The immediate problem is to achieve miniaturization, using fibre optics elements as means of constructing the interferometer which is the essence of the instrument.

mately be saleable, they insist that they can fairly be compared with the Bell Telephone Laboratories in New Jersey because of their willingness to take on basic research.

The laboratory also boasts of close links with the university system, pointing to its usual loss of one or two senior researchers to university chairs each year. And even the scientists and engineers who leave for jobs elsewhere are not an outright loss — they remain customers for Siemens products, it is hoped. □

Helping small businesses

SMALL business is big in West Germany, respected and much cherished. The best-known companies (Bayer, Siemens, Krupp and so on) are huge, and also big spenders on research and development, but everybody knows that the real strength of West German industry rests with the small and middle-sized companies, often too small to support research and development programmes of their own. What can the governments, federal and regional, do for them?

Quite a lot, it seems. West Germany offers a richer menu for encouraging research on a shoestring than any remotely comparable country. Given the way in which graduates of the engineering schools slide into the management of the small companies (and behind the wheel of the accompanying Mercedes), it is natural that they should first turn for help to the academic departments whence they came.

The volume of direct research contract business at the large engineering schools is, however, small. But the constitution of the universities as dependants of the *Länder* makes the connection between the universities and local industry a two-way street. A large but unknown proportion of the grant applications to DFG for engineering projects is stimulated by the needs of small business.

The federal and *Länder* governments also support a more formal mechanism for collaborative research — the Fraunhofer Society (Fraunhofer-Gesellschaft zur Förderung der Angewandten Forschung). This organization maintains some 27 research institutes in West Germany, with interests primarily in solid-state electronics (including defence applications), information processing and the construction and woodworking industries.

Contract research is now the most rapidly growing part of the Fraunhofer Society's work, apparently stimulated by the agreement struck between the federal and *Länder* governments in 1975 on the scale of their support (now running at about a third of the total budget of DM250 million).

In the past five years, the research and economic ministries of the federal government have gone even further and have introduced a number of schemes which amount to direct subsidies for research by small businesses. Small companies letting research contracts to some external research organization (which may be a public laboratory) can apply for grants to cover a third of the cost, but up to a fixed amount. And there is also a scheme of grants to cover the costs of approved in-house research, again within a ceiling.

At the same time, the national research centres are being encouraged to take on research projects for small companies — and given the unaccustomed financial pressures to which they are now exposed,

seem anxious to respond.

The overwhelming response to the research ministry's offer, at the end of last year, of small grants to help with the development of products incorporating microprocessors is one striking illustration of the willingness of small companies to play their part in what has become a self-conscious crusade for the application of research. Having offered grants amounting to DM300 million over three years (up to a maximum of DM800,000),

the research ministry has been swamped with 1,400 applications in the first few months.

The common explanation for this enthusiasm is nothing if not encouraging. What people say is that West German companies, and especially the smaller among them, have awakened to the consequences for them in the present hiatus in the economic miracle and in the challenge from Japan. One small metal-working manufacturer at this year's Hannover Fair put the point simply: he reckons he has at most three years in which to redesign all his products.

Research for sale

MOST stands at the Hannover Fair attract visitors either by means of something that moves or by means of a young woman (rarely a man) sitting at a keyboard hitched to a computer or the like. Dr Jürgen Schulte-Hillen, by contrast, puts himself on show. From morning to night, he sits at a small table seeking to interest potential clients in the services of his small company as an adviser on research and development. Half-way through last month's fair, he was well on the way to laryngitis.

Management consultancy is not, of course, new in West Germany, while organizations such as Battelle (whose Frankfurt establishment includes one of the largest laboratories in West Germany)



Schulte-Hillen predicts a vigorous response to the challenge from Japan

will not merely advise a company on its need for research but will carry out the work on a contract basis. Schulte-Hillen, however, reckons that he has found a unique niche in West German industry.

His small company, now ten years old and employing only 20 people, deals principally with small and medium-sized companies. Its strong suit is to provide advice on how, in a client's operations, research and development might lead to a new product or process. Schulte-Hillen does not himself carry out the work, but will instead arrange a contract between the client and some research establishment, supervising progress much as an architect will breathe down a builder's neck. In the process, the argument goes, the managements of small companies learn what research and

development can accomplish — training in research management, he calls it.

So what (if anything) is wrong with the state of science in West Germany? Schulte-Hillen was for six years head of project planning at a national aerospace laboratory (Deutsche Forschungs und Versuchsanstalt für Luft und Raumfahrt, see page 266) before setting up on his own. He believes that the national laboratories and Max Planck institutes are "highly qualified" institutions with deservedly high reputations, but that they are not flexible enough and that they should have closer links with industry or the universities, as appropriate.

Schulte-Hillen also shares the view common at least among those who graduated before the 1970s that the university reforms have been "a great mistake". He regrets that they have created two classes of universities in engineering, Aachen at one end of the spectrum and Bremen (everybody's whipping-boy) at the other.

The Japanese challenge to West German industry is preoccupying but not depressing. The reason for the Japanese success, Schulte-Hillen believes, is that they have set out to make well-engineered products for a mass market. Except in a few fields, German industry, based as it is on medium-sized companies, is not naturally well placed to compete.

But, in Schulte-Hillen's view, the climate is changing. The past few years have been a shock for West German industry, and the West German automobile industry for one is now bent on becoming competitive again by ensuring good design, high-quality and low costs.

Another sign of the changing climate, Schulte-Hillen believes, is the response of West German industry to the federal government's announcement last year of a programme of small grants (up to DM 50,000) to small companies with development projects intended to use microelectronic devices in novel ways. The applications received since January this year apparently already exceed the DM 300 million originally set aside for the next five years — and one suspects that Schulte-Hillen has written many of them.

Research labs galore

THE legend, according to one senior official of the federal government, is that those who planned the reconstruction of West German science after the war deliberately decided to take over the conspicuous institutions in what were then the obvious models for the administration of science. So now there are research councils (DFG) on the British pattern and national laboratories, as in the United States. The Max Planck Society, however, is special and indigenous.

Whatever the explanation, large laboratories are now an important part of the West German scene, with the establishments run directly by the ministry of research and technology most prominent among them. Altogether, these twelve establishments employ more than 16,000 people and cost the ministry close on DM1,700 million a year.

The laboratories are a mixed bag, including as they do the Cancer Research Centre at Heidelberg (see page 267) and a centre for biotechnology research at Braunschweig (which employs fewer than 300 people). There is a case for thinking that the Cancer Research Centre would fit more comfortably under the wing of some part of the federal government more directly concerned with medicine.

The biotechnology laboratory, on the other hand, originally founded to meet the needs of the fermentation industries, now has a distinguished group of molecular biologists working on such projects as the transfection of cells in culture by gene fragments including the gene of beta-interferon. The laboratory is likely to be one of the beneficiaries of the DM70 million that the ministry of research has to spend this year on various aspects of biotechnology. It remains to be seen how far and how fast the laboratory will move along the path towards commercial exploitation. (As it happens, the laboratory was founded in 1968 with a grant from the Volkswagen Foundation.)

For the rest, the national laboratories range from largely academic establishments including the particle physics laboratory DESY at Hamburg (see page 270) and the plasma physics laboratory at Munich (see page 271), which is also a Max Planck institute, to the nuclear establishments at Jülich and Karlsruhe and the sprawling aerospace research organization centred on Cologne. They are collectively represented in Bonn by an Association of Big Science Establishments (or AGF for Arbeitsgemeinschaft der Grossforschungseinrichtungen).

As elsewhere, AGF's West German members are having painfully to adjust to changed economic circumstances. As recently as 1980, the laboratories were hatching a scheme for employing 700 younger scientists in specially created posts — a temporary expedient to keep young people in research and the research

ministry's equivalent of the Heisenberg programme run by DFG. Now, like other government establishments, the national laboratories are having to reduce their staffs by 7.5 per cent over the next five years. Even so, AGF hopes to maintain the validity of its boast that 350 graduate students from West German universities earn their doctorates at its member establishments.

The process of contraction should not be as difficult as some fear. Natural wastage by retirement, death and so on runs at about one per cent a year, while the rate of resignation by people leaving for other jobs is said to average 4 per cent a year. The question that naturally arises, however, is whether there should be some more radical change in the pattern of this substantial research effort.

Much, no doubt, will depend on the success of these laboratories in persuading the general run of West German industry that developments incidental to what would be called, in the United States, their missions are of commercial value. Beneath an elaborate green tent-like structure at the Hannover Fair this year, AGF orchestrated an impressive display by its members of technology that may have a wider use.

Thus the Karlsruhe laboratory now boasts of a piston-driven pump for liquid helium, the Jülich laboratory of novel ceramic heating units (offshoots of its work on the development of equipment for installation in high-temperature reactors) and the aerospace laboratory claims already to have had success overseas in licensing its designs for fuel-oil burners. (Their high efficiency depends on the way in which droplets of fuel oil are vaporized by combustion gases before being ignited.)

The two nuclear laboratories at Karlsruhe and Jülich are of particular interest because of their close involvement, over past years, in the West German development of civil nuclear reactors. (Other member laboratories of AGF have an interest in nuclear affairs, including the GSF laboratory in Neuherberg near Munich concerned with problems of the geological disposal of radioactive wastes, the Hahn-Meitner institute in Berlin with an interest in radiation chemistry and the GKSS centre at Geesthacht-Tesperhude in northern West Germany which is a monument to enthusiasm in the early 1960s for nuclear-propelled ships.)

Both establishments have long since outlived their original remits. The Jülich establishment, for example, was founded (in 1956) by the *Land* government as a nuclear research facility for the universities of Nordrhein-Westfalen but was converted into a national laboratory in 1968. It is still responsible for the development of the technology of high-temperature reactors, as Karlsruhe is responsible for fast-reactor technology. (The plan is that Karlsruhe will shed 70 of its 270 fast reactor people in five

years or so, when the prototype fast reactor at Kalkar should at last be complete.)

The question never far beneath the surface is whether there will be reactor-development projects with which to continue when these come to an end. For the past two years, even the construction of well-established types of reactors has become a contentious political issue — and not merely in the safe SPD country of Hamburg but in CDU Bavaria as well. Although Chancellor Schmidt was able to avoid the two-year moratorium on civil nuclear construction demanded of him at his party's conference in Munich last month, plainly the political climate is one in which new proposals for major reactor development would not be easily accepted, while the electricity utilities, stung by the research ministry's success at persuading them to contribute extra funds to the cost of the fast reactor prototype, are unlikely to be pressing for further initiatives in this direction.

The present plan seems nevertheless to be that these laboratories should be kept alive on more or less the present scale, with the understanding that new tasks should be transferred to them whenever possible. The principle that it is easier to start a new laboratory than to close one down applies in West Germany perhaps even more rigorously than elsewhere, given the close interest (and the 10 per cent financial contribution) of the *Länder* governments.

AGF is not the source of funds for these laboratories but rather a coordinating mechanism for those national laboratories that happen to come under the wing of the research ministry. Other federal laboratories exist more inconspicuously, again but in partnership between the federal government and the *Land* concerned.

Among these, the geoscience and resources agency at Hannover has made an international reputation for itself with its overseas surveys, especially in developing countries (and has also just completed a thorough survey of groundwater resources and their contamination by pollution for the whole of West Germany). The Tübingen veterinary laboratory similarly has a distinguished academic as well as practical reputation. Conspicuous by its absence in West Germany is the string of medical research laboratories that would be found in most other places — a measure of the dominance of the medical faculties but perhaps also a pointer to the need that medical research should be less fragmented.

On the principle that anything the federal government can do the *Länder* can do independently, there is also a spattering of regional research laboratories on the map of West Germany. Veterinary and geological laboratories are common, but Hesse supports the Sigmund Freud institute of psychoanalysis and Lower Saxony plans to set up a microelectronics laboratory once it has chosen between Hannover and Braunschweig.

What prospects for improvement?

THIS brief survey of science in West Germany is necessarily incomplete. Only a small sample of the important national research laboratories rates is mentioned. Most Max Planck institutes have been overlooked. And much too little has been made of the great wealth of sound biology now flourishing in universities, much of it deliberately fostered by the grant-making agencies such as the Deutsche Forschungsgemeinschaft. It is hoped that these deficiencies can be made good in the months ahead. For what is happening in West Germany, both in laboratories and in the committee rooms that help to shape their work, deserves much closer attention from the rest of the scientific community.

Incomplete though they may be, the preceding pages nevertheless confirm first impressions. Both researchers and those who manage their affairs are unsure of themselves, concerned that the substantial commitment of West Germany to research and development may be yielding less than it might. Comparisons with the United States are constantly preoccupying and rarely confident, which is why the doings of the particle physics laboratory at Hamburg (see page 270) stand out. Here at least is one laboratory not depressed by pointless calculations about the award of Nobel prizes. (For what little worth they have, the figures show that there have been 16 Nobel awards to West German nationals since the Second World War, compared with 124 and 42 awards to American and British nationals respectively.) The important question is how such a state of grace can be brought about elsewhere.

One of the dangers in West German introspection about the quality of research and development is that the distinctive and valuable features of the system will be undermined. Thus for decades other European countries have envied the way West German *Technische Hochschulen* forge such close connections with particular industrial sectors that both partners benefit immensely, as does the West German economy as a whole. Whenever British politicians take up the gloomy question "Why is Britain not more productive?", there is certain to be somebody to remind them that it might be different if British universities chose to follow this West German practice. The report (on page 275) from Aachen shows this practice still flourishes. The snag for those who look for proof of success in the international award of honours, is that research in the design of machine tools is neither one of the topics mentioned in Nobel's notorious will nor a productive source of references in the primary journals. And while there may be some who complain that the education offered by the hot-houses among engineering schools may be undesirably narrow, or needlessly demanding, the success with which the graduates of these schools are able to make their way in West German industry is surely a proof that the engineering schools and West German industry have found a productive pattern for their relationship.

Elsewhere, however, the university system is in a mess. The reforms of the past quarter of a century have had the benefit of making sure that tenured professors cannot behave as tyrants, and have helped also to give West German universities a sense that their corporate identity extends to all who work in them, but only at the cost of licensing an intolerable and demeaning bureaucracy. Is it any wonder that people seeking a career in research prefer to work elsewhere, at a Max Planck institute perhaps, or even in the United States? The most obvious difficulty is that ridding the system of this blight cannot be accomplished by the universities themselves, only by the twelve governments of West Germany.

Sooner or later, something will have to be done to allow the universities to match their intake of students in all fields to their capacity to teach them properly. The pretence that all universities are educationally and intellectually equal will have to be abandoned. The universities must be rid of the legal harassment by students and would-be students with which they are now plagued, and should be free to decide for themselves the composition of the internal committees that manage their affairs.

Nobody pretends that such steps could be taken easily, for they would offend against cherished constitutional principles. But to fail to take them is to perpetuate bumbledom and inefficiency.

There is also a need to change the present balance between the support for basic research by the principal grant-making agencies. The most glaring need is for a closer link between the 6,000-odd researchers who work in the Max Planck institutes and the much greater number of professional scientists who work in universities. Although the Max Planck Society acknowledges the need that new institutes should be sited near universities, although many institutes have members who work on common problems with university colleagues, and although senior members of the institutes are eager (and welcome) teachers at their local universities, the plain truth is that the institutes attract many of the most able younger scientists — and then provide many of them with an environment in which they can securely become less productive. The resentment that has sprung up between the two groups of people is not good for the research enterprise.

There is a need, less obvious but just as urgent, for adjusting the present balance of support for research within the universities. One of the unusual features of the West German system is that the bulk of the cost of university research is met directly by the *Länder* (regional) governments, with the Deutsche Forschungsgemeinschaft playing a relatively minor role. (The official estimate of a ratio of four-to-one is probably an over-estimate, but is not easily verifiable.) At many universities, Heidelberg for example, tenured professors look to the general budget for research support, but more junior colleagues must take their chances with DFG. Could this be why people returning to West German universities after a promising start elsewhere are so often said to slump into inactivity? The doctrine of the unity of research and teaching is wholly admirable but there is a danger that much of the research support now channelled from the regional governments to university researchers finds its way into projects that would not survive the rigours of peer review. This may also explain why the de-deification of the old-style professors has not been matched by a corresponding sense of liberation among junior colleagues. Given the generality of the observation that, compared with their equivalents elsewhere, younger scientists in West Germany are less adventurous — less likely to be disastrously wrong or brilliantly right — a more selective way of offering larger dollops of research support seems necessary. The general anxiety about clinical research argues in the same direction.

The problems peculiar to West Germany appear principally to affect basic research. There are also the familiar problems of what to do with research establishments that have lasted longer than the problems they were intended to solve, arguments about research strategy (how much to spend on solar energy development?) and anxieties about political interference (should a new laboratory go in one place rather than another?). West Germany is not worse afflicted than other places, while the scale of its research enterprise, and the skill of its practitioners, imply immense advantages. So has not the time come for the research community to insist that what it knows to be wrong should be put right? The paradox of West Germany is that the elaborate hierarchy of policy-making bodies that has evolved since the Second World War is somehow incompetent to challenge prevailing ideologies, even those that lead directly to the absurdities now manifest in the university system.

So the hunt goes on for other explanations of why West German science is not the glittering enterprise it should now be. It is like a heavy smoker with a chest infection seeking a psychosomatic explanation for his complaint. Although West German science may to some extent still be made tentative by the awful experience of what is euphemistically called "the period 1933-45", and by the sheer newness of the federal republic, what matters now is that each year increases the distance from that time — and brings a new cohort of productive people to adulthood.

NEWS AND VIEWS

Crust to crust, basalt to basalt

from Peter J. Smith

As the author of Ecclesiastes might have put it, of the making of many geochemical hypotheses for the workings of the Earth's interior there is no end. Or so it seems. Those who don't pay the closest possible attention to the flow of geochemical thinking — and many of those who do, for that matter — can hardly be anything but bewildered at the sheer quantity of it all and the seemingly infinite number of paradoxes and inconsistencies it represents. New sites are continually being investigated, only to provide solutions to some problems whilst revealing fresh anomalies. New methods are continually being introduced, only to fulfil some of their promise but present additional difficulties. New hypotheses are continually being proposed, only to reconcile some data at the expense of mutually exclusive hypotheses that reconcile other data. To the outsider, ever more research must look suspiciously like the source of ever more confusion, offering the reminder that the Earth's interior only looked remarkably simple when next to nothing was known about it. The much-needed global model that succeeds in reconciling the mass of conflicting observational evidence seems as far away as ever.

The new model put forward by Hofmann and White¹ hardly fills that all-embracing role, but, if valid, it should go a long way towards explaining some of the apparent contradictions that have recently come to the fore as a result of the increasing attention being paid to oceanic island basalts (OIB). Not least among the inconsistencies is the fact that, whereas OIB are 'enriched' (that is, with respect to 'primitive', bulk-earth, chondritic material) in incompatible elements such as K, Rb, U and Th and the light rare earth elements (LREE), Nd isotopic data seem to suggest that the source of most OIB is 'depleted' in LREE. For some time now, the differences between OIB and mid-ocean ridge basalts (MORB) have been interpreted as indicating distinct sources in the mantle; and under those circumstances it was possible to hold (not that everyone did) that the OIB were derived from primitive material (such as the lower

mantle, if primitive it be) and the MORB came from a relatively depleted source (for example, the asthenosphere, if depleted it be). But the Nd data would seem to rule that out.

So how can LREE-enriched OIB be, or appear to be, derived from an LREE-depleted mantle source? Wasserburg and DePaolo² have suggested that perhaps the Nd isotopic data only indicate a non-primitive source for OIB because the initially primitive material gets contaminated with depleted MORB source material in the upper mantle. But that appears to conflict with Pb isotope and other evidence. Menzies and Murthy³, among others, have proposed that metasomatism enriches the OIB source before melting. But there appears to be no evidence for that, at least from the source material itself. Even earlier, Gast⁴ had attempted to account for the enrichment of OIB by supposing that primitive OIB source-material undergoes less melting than MORB source-material. But the degree of melting this requires is probably far lower than most petrologists would countenance.

Hofmann and White cut right through these proposals and objections. They first state that the OIB source cannot be primitive — a conviction based on the "rather conclusive" evidence that (1) no primitive source could give rise to enriched OIB without an unacceptably low degree of melting, and (2) a primitive source is inconsistent with the isotopic data (Rb, Nd, U, Th and so on). Next, they express their faith in Morgan's mantle plume hypothesis⁵, because they find "his arguments as persuasive today as they were ten years ago and because . . . no viable alternative model has been proposed that would explain the kinematic and geochemical peculiarities of 'hot-spot' volcanism". They then look round for a possible source of the non-primitive material that forms the mantle plumes, and

come up with the bold suggestion that it is ancient, subducted crust.

As might be expected, this is not the first time that the fate of subducted crust has been considered. Ringwood⁶, for example, suggested that such crust might sink to the base of the mantle and thus be lost permanently to the convective system. Tatsumoto and Knight⁷ and, more recently, Anderson⁸ have proposed that subducted crust is recycled to form new oceanic crust, including OIB. What Hofmann and White have done, in effect, is to combine components from both these views into the proposal that subducted crust sinks to the bottom of the mantle whence it ultimately rises again in the physical form of mantle plumes.

As new, initially basaltic, oceanic crust moves away from ridges it is subjected to hydrothermal alteration, undergoes low-temperature alteration and accumulates sediments; and as it subducts it experiences metamorphism and partial melting. Even so, its bulk composition is still likely to be more or less basaltic, and its density will almost certainly be higher than that of upper mantle material and probably higher than that of lower mantle material too. It therefore sinks until it reaches a level of density compensation (presumed here to be as deep as the core-mantle boundary), shedding the more refractory part of the lithosphere as it does so. Once at its new site, where it builds up to thicknesses of 100 km or more, it begins to heat up, partly because of radioactive heat production within it and partly through heat transfer from the core. As the temperature rises the layer becomes unstable, and diapirs (plumes) ascend into the upper mantle where the material melts, rises to the surface and forms oceanic islands or continental hotspots as appropriate.

Hofmann and White go to some lengths to demonstrate that such behaviour is thermally and mechanically plausible. But something more than that emerges, for the (admittedly crude and assumption-ridden) calculations also give a hint of the time scale involved. The time taken for the once-crustal layer at the base of the mantle to develop instability seems to be as much as

Peter J. Smith is a Reader in the Department of Earth Sciences, The Open University, Milton Keynes MK7 6AA, UK and editor of Open Earth.

one to two billion years, implying that the material now rising as mantle plumes was oceanic crust as long ago as the Proterozoic. In this connection, it is interesting to note that apparent mantle isochrons for recent OIB commonly yield ages of about 1.8 (Pb) and 1.6 (Rb/Sr) billion years. Moreover, Morgan also suggested that plumes may actually initiate seafloor spreading/upper mantle convection by breaking up plates and thus allowing the passive upwelling of mantle material. Putting all this together, it is tempting to envisage an Earth in which periods of plume-triggered mantle convection alternate with intervals of mantle stagnancy during which the stored, subducted crust gradually heats up towards instability.

The first of the geochemical conclusions to be drawn from all this is that, by definition, OIB source-material cannot be primitive. On the other hand, the exact bulk composition of the material is difficult to specify. As the crust subducts it may or may not take sediment with it, it will be metamorphosed to an uncertain extent, and dehydration and partial melting will remove an unknown quantity of incompatible elements. At some point it will then be converted to eclogite and the less dense, depleted part of the lithosphere will separate and return to the MORB reservoir (presumably the asthenosphere). It seems unlikely, however, that these processes will be anything like thorough enough to remove all the incompatible elements — a conclusion for which there is some support from a consideration of what happens to K during subduction and magma production in island arcs. In other words, it would seem that when the subducted crust reaches the lower mantle it is still enriched.

The problem of having to explain how enriched OIB are derived from a depleted source is thus removed; the source is not depleted. What, then, of the Nd isotopic data, which seem to demonstrate otherwise? At this point it is necessary to bear in mind that, according to the Hofmann-White hypothesis, modern OIB are derived from Proterozoic crust — that is, Proterozoic MORB. Studies of mantle-derived basalts have shown that Nd/Sm ratios in large parts of the mantle have become progressively depleted. Thus Proterozoic MORB were less depleted than are modern MORB; and, as a result, modern OIB would be expected to have variable but generally lower $^{143}\text{Nd}/^{144}\text{Nd}$ ratios than modern MORB — which they do. Moreover, a MORB source would be able to produce OIB with 'normal' degrees of melting — 10 to 30 per cent for tholeiites.

As for the major elements, Hofmann and White point out that the idea of an OIB source of an essentially basaltic composition is "not dear to petrologists", the prevailing view being that basalts are produced by the partial fusion of peridotite. There are indeed problems in

envisaging the generation of basalt from eclogite; but they may not be insuperable in this case insofar as the Hofmann-White model does not insist upon a source of pure eclogite. The subducting and sinking crust may not shed quite all of its associated refractory lithosphere. The incorporation of, say, 10–20 per cent of mantle peridotite would be sufficient to overcome the geochemical objections to an eclogite source (such as the fact that most OIB are olivine saturated). Moreover, there is bound to be some interaction between the ascending mantle plumes and the upper mantle peridotite through which they pass. None of this would change significantly the density, incompatible element composition and heat production in the rising plume material but it would easily provide sufficient olivine and pyroxene to bring the major element (and compatible element) composition into line with observation. To this extent, therefore, major element abundances do not impose strong constraints on the new model.

It is a measure of the disarray in which geochemistry finds itself that almost any

sentence of substance in any article on the subject can, and is likely to, attract perfectly legitimate objections. Hofmann and White's work is unlikely to be an exception. Indeed, they admit that their model is an extreme one, "a broad target for criticism", a bold idea that may have to be modified if some of the details fail to correspond with future observations. Few people, however, would deny the importance of bringing the question of OIB-MORB differences to the fore. Many, if not most, geochemical models of the mantle have hitherto ignored OIB, largely on the grounds that they are volumetrically small in comparison with MORB. What Hofmann and White have done is show that relative volume may be no measure of scientific significance. □

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The gaps in the fossil record

from David E. Schindel

THE fossil record has been both a burden and a blessing to evolutionary biologists — a blessing because the stratigraphical order in which fossils are arrayed provides broad proof of change with time, but a burden in that the gradual morphological transitions between presumed ancestors and descendants, anticipated by most biologists, are missing. Darwin and most of his followers have resolved this dilemma by accepting the blessing and dismissing the burden as an unfortunate but inherent limitation in the fossil record resulting from varying rates of sediment deposition.

In their much cited paper, Eldredge and Gould (ref. 1; see also ref. 2) re-examined the discrepancy between palaeontological patterns and biological processes. They argued that despite the imperfections in the fossil record, the pattern of abrupt appearances of new species might be a faithful rendition of speciation events, if viewed on a geological time scale. They contrasted two models, phyletic gradualism and punctuated equilibria. In the former, new species arise through the steady accumulation of microevolutionary change over significant spans of geological time. The discrepancies between generation-to-generation change and the observed palaeontological pattern would

therefore be real, since most species appear abruptly in the fossil record. In the punctuational view, species persist more or less unchanged throughout their duration but infrequently and abruptly give rise to new forms. The long spans of morphological stasis within species would thus be a literal record, not an artefact of an imperfect record. The discrepancy would be more perceived than real, in this view.

Over the past ten years, microstratigraphical studies have appeared which document fine-scale patterns of change. Using the finest scale of sampling possible, investigators have attempted to test the reality of the discrepancy between microevolutionary changes (visible during a human lifetime) and the palaeontological patterns by approaching the time scale on which biological processes operate. These field studies have faced two serious challenges in the past year. First, the scale on which evolutionary patterns are documented is critical, because "one man's punctuated equilibrium may be another's evolutionary gradualism"³, and "stepwise changes can be made to appear gradual if a coarse enough time scale is selected"⁴. The second and more serious challenge states that the stratigraphical record, as a whole, is so incomplete that fossil patterns are meaningless artefacts of episodic sedimentation⁵. This article provides a response to these challenges by outlining procedures for evaluating the level of time resolution obtained in

David E. Schindel is a Curator of Invertebrate Fossils in the Peabody Museum of Natural History and an Assistant Professor of Geology at Yale University, PO Box 6666, New Haven, Connecticut 06511.

microstratigraphical studies, and the quality of the patterns they document.

Three criteria are necessary for evaluating temporal resolution in the fossil record. *Temporal scope* is the total time span over which the pattern is documented. *Microstratigraphical acuity* is the time span represented by each individual fossil sample. *Stratigraphical completeness* is the proportion of the total time span (temporal scope) that is represented by strata.

Temporal scope is estimated with the common tools of stratigraphy, ultimately being established by radiometric dating techniques. Acuity and completeness estimates are based on short-term sedimentation rates, which document the rate at which sediments accumulate without gaps. Sedimentation rates based on longer-term observations include periods of non-deposition and erosion, and are therefore lower than short-term rates in similar settings. Brief periods of non-deposition or erosion are undoubtedly common, but are less likely to be described in the literature than are brief periods of active accumulation. The pattern of lower rates of sediment accumulation with longer spans of observation time has been documented in two recent compilations^{6,7}.

If individual fossil samples are taken from stratigraphical intervals free of evident sedimentological breaks (such as scoured surfaces, hardgrounds, bedding planes, attritional shell and bone beds), then dividing the sample thickness by a short-term sedimentation rate typical for that depositional setting (over, say, 100 yr) gives an estimate of acuity that assumes the interval of strata accumulated without interruptions greater than 100 yr (see refs 6 and 8 for further explanation). Completeness is estimated by first dividing the

thickness of the entire strata by the appropriate short-term sedimentation rate, and the time span so derived is then divided by the temporal scope of the entire sequence. This completeness ratio represents the portion of the temporal scope represented by active accumulation of sediment, that is, if the entire sequence accumulated without interruptions greater than the time span of observation for the short-term rate used in the calculation. Sadler⁷ provides a detailed and elegant treatment of this procedure.

The table presents data on the stratigraphical thickness and temporal scope of seven published microstratigraphical studies⁹⁻¹⁵, along with my estimates for the acuity and completeness inherent in each. Three points emerge from this review of published studies. First, there is a trade-off between scope, acuity and completeness: a study can provide fine sampling resolution, encompass long spans of geological time, or contain a complete record of the time span, but not all three. Second, some microstratigraphical sampling schemes can provide acuity that approaches the time scale of biological processes (decades to centuries), if individual samples are collected with an eye to avoiding sedimentological breaks⁶. (Of course, extra caution is necessary in strata that show signs of bioturbation or resuspension, which act to obscure evidence of breaks.) Third, it is most difficult to evaluate evolutionary patterns in studies with high acuity (minimum of time per sample) and low completeness, unless the investigators document where the breaks occur in the sequence, and attempt to sample between the gaps. In so doing, a procedural trade-off is made by decreasing the scope of the sampled

interval, within which acuity and completeness can remain high. This seems to be the case for the study by Williamson¹⁵, and the within-cycle sampling by Schindel¹⁴. The patterns distilled from these relatively short, complete sequences can be read directly, and can be calibrated in years using short-term sedimentation rates. Without specific knowledge of where the breaks are located it is difficult to judge whether the other documented evolutionary patterns are gap-filled (and therefore may be artefacts of varying sediment input), or if they are relatively gap free, with the unrepresented time concentrated above and below the critical sampled portions of the sequences.

The debate over tempo and mode should proceed beyond the stage of arguing, in terms of generations, how fast is fast, and how slow is slow. It seems possible to estimate the quality of local stratigraphical sequences and the level of sampling acuity achieved in each. The gaps in the stratigraphical record are neither scattered so randomly nor hidden so well as to render the entire fossil record useless. I would therefore replace van Andel's⁵ counsel of despair with a call for caution in sampling, and greater awareness among palaeontologists to the progress being made in genetic stratigraphy and facies analysis.

One other point emerges from this treatment of the gaps in the record. Most sedimentological breaks reflect changes in physical environmental conditions (water depth and current regime, sediment influx, carbonate productivity). Certainly, when one considers the large proportion of unrepresented time in the studies reviewed here, it seems very likely that changes in habitat conditions are scattered throughout stratigraphical sections. For this reason alone, one might question the wisdom of extrapolating the generation-to-generation processes witnessed by biologists (primarily during periods of stable conditions) up to geological time spans.

Contrary to a recently expressed⁴ and commonly held opinion, the debate between the punctuated and gradual viewpoints is not an argument over rates of change, but an argument over the persistence of rates. Many biologists assume that the generation-to-generation microevolutionary processes they witness are typical short segments of trends that persist through geological time. Using this assumption, morphological stasis can be explained as the result of persistent stabilizing selection, and gradual trends in size or shape would result from sustained directional selection. But the present treatment of the gaps in the fossil record calls into question this assumption of persistent rates, stable environmental conditions and sustained selective regimes. Stasis may result if directional trends are short-lived and frequently reversed. Long-term trends may be processions of morphologically distinct and separate populations, rather

Temporal resolution achieved in seven published microstratigraphical studies, evaluated with three criteria defined in the text

Subject (ref.)	Stratigraphical thickness(m)	Temporal scope(My)	Sample thickness(m)	Microstratigraphical acuity(yr)	Time represented (yr)	%Stratigraphical completeness
Eocene mammals (9)	520	3.5	10	4,000	980,000	28
Permian forams (10)	200	12	<1	600	500,000	4
Neogene radiolaria (11)	5	1.9	<0.01	40	35,000	2
Neogene forams (12)	200	8.3	0.02	80	1,700,000	23
Jurassic ammonites (13)	14	1+	<0.01 (e)	40 (e)	28,000	3
Pennsylvanian snails (14)	1,300 (a)	27	<10	5,000	9,300,000	34
	10 (b)	(5kyr?)	<0.1	50	(5,000?)	(100?)
Plio-Pleistocene molluscs (15)	265 (c)	0.4	0.25	170	180,000	45
	110 (d)	0.1	0.25	170	73,000	73

Stratigraphical thickness, temporal scope and sample thickness are taken directly from original studies. Microstratigraphical acuity was calculated by doubling each sample thickness to correct for compaction, then dividing by a short-term accumulation rate for uncompacted sediment in that environment estimated from compilation of rates by Schindel⁶; these rates were based arbitrarily on 100 yr periods of observation, and therefore assumed that samples contained gaps no greater than 100 yr. Time represented was estimated by doubling the stratigraphical thickness to compensate for compaction, and dividing by the sedimentation rate appropriate for that environment and the level of sampling acuity, giving the time represented by each entire sequence if it contained gaps no greater than the time span of a sample. Completeness is the percentage of the temporal scope represented by active sediment accumulation at this level of sampling resolution. Note trade-off between scope, acuity and completeness.

(a) Among-cycle study spanning Middle and Upper Pennsylvanian time.

(b) Within-cycle study of a single mudstone interval in the Middle Pennsylvanian. The interval is entirely within a single fossil zone, so temporal scope and completeness cannot be estimated by independent evidence, indicated by (?).

(c) Entire Koobi Fora Formation.

(d) Lower Member, Koobi Fora Formation.

(e) Many samples were collected from bedding planes, and are probably time-averaged attritional assemblages. Estimates presented assume 1cm sample thickness within which breaks are not found.

than gradual modifications within a single standing population.

I do not question the reality of short-term directional changes, but I point out the evidence that abounds in the fossil record for habitat shifts, local extinctions and the general lack of persistence in physical conditions. One might assume that changes in physical habitat conditions occur slowly and imperceptibly, allowing any particular biota to migrate passively within geographical limits of the moving habitat. But this view would be an intuitive notion, not a proven point. The effect of habitat shifts on populations over geological time remains an open question. Microevolutionary processes probably operate within the constraints imposed by higher-order processes, which define the distribution and duration of habitable area

available to organisms. The gaps in the record suggest that these processes disengage the short-term fate of individuals from the longer-term fate of populations, species and higher taxa. □

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The age of galaxies

from M. G. Edmunds

ALTHOUGH it has become apparent in recent years that there are quite a few observational constraints on cosmological models, it remains true that facts in cosmology are rare. Any new information must be greeted with delight, and two recent investigations of time and distance scales in the Universe are particularly welcome.

The observational evidence for the evolution of galaxies over cosmic time dates back to the interpretation of radio source counts. Subsequently the so-called 'luminosity-volume' test was applied with considerable success to suitable samples of quasars, and it was concluded (well reviewed by J.V. Wall in *Phil. Trans. R. Soc. A* **296**, 367; 1980) that very active objects like quasars and radio galaxies were far more numerous in the past. It is not suggested that these sources have now completely disappeared, but rather that many galaxies which are comparatively quiescent at the present time must have been much more active at earlier times. The general indications are that the effective number of certain kinds of sources was greater by a factor of perhaps 1,000 when we look back to redshifts between 1 and 3 (corresponding to about 1/3 to 1/5 of the present age of the Universe, assuming a standard expansion model with fairly low overall density of matter).

It has been realized for several years that back beyond a redshift of 3 there may well be no further increase in source numbers, but the observational problems of carrying out a survey for objects that far away are severe. A significant step backwards (if that is not an impolite way of describing the work!) has been made by P.S. Osmer (*Astrophys. J.* **253**, 28; 1982). He has searched systematically for quasars with

redshifts greater than 3.5 (that is, looking back beyond 1/5 of the age of the Universe) in an area of 5 square degrees in the sky by using a special spectrum disperser in front of photographic plates. The disperser, a grating prism, stretches out the images of stars and galaxies into small spectra of just sufficient resolution to allow possible quasars to be identified by their strong emission lines. These faint quasar candidates were then examined at higher resolution with a conventional telescope/spectrograph combination. No quasars were found in the search area between redshifts 3.7 and 4.7 (the limit of the technique). Of course the survey has a faintness limit, but previous work in the redshift interval 2.5–3.5 suggests that at least nine quasars should have been discovered even if the space density of objects were constant beyond redshift 3.5. The fact that none was found implies that the density must decrease significantly. The lack of quasars in this particular area of sky could be attributed to a chance fluctuation in spatial distribution, but if we assume a Poisson distribution on the sky, then for an expected number of nine objects in the area, the variance is nine and the detection of none is a very highly significant result!

The importance of the definite demonstration of a decrease in space density lies in the implication that violent activity in galaxies starts at a time corresponding to around redshift 3.5. Since the activity requires a galaxy we can conclude that galaxies must exist at that time. Furthermore, as activity is thought to begin fairly rapidly after the actual formation of the

galaxy as a discrete entity of stars and gas, it can be argued that we are seeing back to the epoch (about 1/5 of the age of the Universe) at which galaxies form.

Despite his careful area-limited search, Osmer must have been disappointed that he did not beat the record for the largest redshift discovered, set at 3.53 about a decade ago. It is perhaps a little ironic that very soon after Osmer's paper was published, a press release appeared from workers in Australia (B. Peterson, A. Savage, D. Jauncey and A. Wright), reporting that optical spectroscopy of the radio source PKS2000–330 shows that it is a quasar with redshift 3.78. This in no way vitiates Osmer's result, since it is not at all surprising that there are some quasars beyond redshift 3.5 — but there are not very many of them.

How long ago, in real terms, was this epoch of quasar and, by inference, galaxy formation? The expansion time scale of the Universe has been a controversial issue for many years, the uncertainty arising from the great difficulties of accurately measuring distance in astronomy. The conventional chain of reasoning is a long and indirect one, passing from the parallax measurements of the nearest stars, out to various size and brightness indicators in galaxies of known redshift. The number determined observationally is the Hubble constant, H_0 , and the two major determinations of its value are either 50 km s⁻¹ Mpc⁻¹ or 100 km s⁻¹ Mpc⁻¹, depending on whether the Universe is viewed from California or Texas. The pragmatic astronomer might be tempted to take a mean value between the two, and some support for this approach comes from a recent determination of the distance to supernova explosions in distant galaxies by W.D. Arnett (*Astrophys. J.* **254**, 1; 1982). The extreme brightness of supernovae makes them ideal probes of distance and although distance estimates have been attempted before, using kinematic models of their expansion, this is the first time that a dynamical model for type I supernovae has been used. The model is admittedly very simplified, and aims at estimating the intrinsic brightness of the supernova on the basis that the luminous energy is supplied by radioactive decay of ⁵⁶Ni, freshly synthesized in the explosion. The distance can then be inferred from the supernova's apparent brightness. From a set of supernovae in several clusters of galaxies, a value for H_0 of 70±10 is deduced, which lies nicely between the disputed values. The implied age of the Universe is then about thirteen billion years, again assuming a fairly low mass density. Arnett stresses that his value for H_0 should not yet be taken too literally, since there are many refinements to his simple supernova model that need investigation. Nevertheless, the age of galaxies would then be of the order of ten to eleven billion years, an acceptable time scale compared with present estimates of the ages of some star clusters in the Galaxy,

M.G. Edmunds is in the Department of Applied Mathematics and Astronomy, University College, Cardiff CF1 1XL.

and the age estimates based on comparative abundances of radioactive nuclei. This would at least avoid the problems created by the higher value of H_0 of $100 \text{ km s}^{-1} \text{ Mpc}^{-1}$, which suggests a Universe age of nine billion years com-

pared with star cluster ages which are estimated to be in excess of ten billion years. The lower value of $50 \text{ km s}^{-1} \text{ Mpc}^{-1}$ cannot be ruled out, although the age of galaxies (following Osmer's result) would have to be at least 14.5 billion years. $\square$

150th anniversary of Gauss's first absolute magnetic measurement

from S.R.C. Malin and D.R. Barraclough

ON 26 May 1832, the horizontal component of the Earth's magnetic field at Göttingen was $1.7820 \text{ mg}^{1/2} \text{ mm}^{-1/2} \text{ s}^{-1}$ ($= 17,820 \text{ nT}$). Not particularly remarkable, you might think, except that this was the first ever absolute measurement of the geomagnetic field and its attainment had required much of the armoury of one of the world's greatest mathematicians.

Carl Friedrich Gauss (1777–1855) was a gifted child. His early mathematical feats led his father grudgingly to agree with his teachers that the boy should receive higher education rather than learn a trade, but Gauss was also an exceptional linguist and might equally easily have chosen to study philology. It was the satisfaction he derived in 1796 from demonstrating the construction of a regular 17-sided polygon with ruler and compasses that finally decided him on a career in mathematics. In his doctoral thesis, he proved the 'fundamental theorem of algebra' (the first of his four independent proofs of this theorem), and most of his work at this time was similarly concerned with pure mathematics. Although this continued to be his main interest, he gradually branched out into many other subjects, including applied mathematics, astronomy, geodesy, optics, telegraphy and geomagnetism.

Soon after 1830, Gauss became interested in the adoption of a universal system of units for all physical quantities, and came to the remarkable conclusion that even magnetic intensity could be measured in terms of mass, length and time. With the practical assistance of Wilhelm Weber, professor of physics in the University of Göttingen, he set about devising an experiment to make this measurement. He explains some of his ideas in a letter to the astronomer Olbers written on 18 February 1832.

"I occupy myself now with the Earth's magnetism, particularly with an *absolute* determination of its intensity. Friend Weber conducts the experiments on my instructions. As, for example, a clear concept of velocity can be given only through statements on time and space, so in my opinion, the complete determination of the intensity of the Earth's magnetism requires to specify (1) a weight = p , (2) a length = r , and then the Earth's magnetism can be expressed by $\sqrt{p/r}$."

The experiment came to fruition three

months later, after Gauss had slightly revised his dimensional arguments. The apparatus required is very simple — two bar magnets (A and B), one single-filament suspension in which either magnet can be fitted, a ruler, a clock and two weights. The method is also simple, though a number of refinements are required if its full accuracy is to be realized. The first part is the vibration experiment in which magnet A is suspended horizontally, and its period of oscillation either side of magnetic north measured. The period T is related to the magnet's moment of inertia, I , its magnetic moment, M , and the horizontal intensity of the geomagnetic field, H , by

$$T = 2\pi \sqrt{\frac{I}{MH}}$$

Thus, if I is known, we can infer MH . Gauss deduced I by adding known increments to it in the form of weights at known distances from the suspension, and noting how this affected T . In calculating I from the several different values of T and ΔI , Gauss used a powerful technique which he had developed himself, the method of least squares. He also took care to adjust T to the value it would attain with vibrations of infinitesimal amplitude, as the equation is strictly valid only for that case.

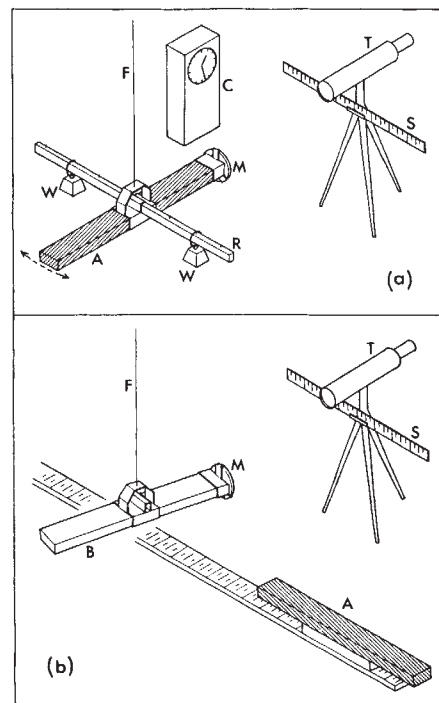
The second part is the deflection experiment in which the ratio M/H is determined by suspending magnet B and noting its angular deflection from magnetic north when magnet A is placed at a known distance to the east or west. This requires a knowledge of the way in which the magnetic intensity due to a bar magnet falls off with distance. Gauss deduced this from first principles, showing not only that the intensity due to a dipole depends on the inverse cube of the distance, but also that one additional term is both necessary and sufficient to allow for the finite length of the bar magnet. He determined the parameters by measuring the deflection with magnet A at different distances, again solving by the method of least squares.

From a knowledge of MH and M/H ,

both M and H can readily be deduced.

Because of secular change, it is difficult to assess the accuracy of Gauss's original observation but, from internal consistency and backward extrapolation of the trend from later observations, it seems likely that it was within one per cent of the true value. With only minor modifications, Gauss's method continued to be the standard way of measuring H at magnetic observatories and in the field until the 1920s, and it is still in use at some observatories. Nowadays, absolute magnetic intensity measurements are usually made with a proton magnetometer. This gives the answer to an accuracy of about 1 part in 10^6 in a few seconds.

This was not Gauss's only contribution to geomagnetism. He later applied yet another of his inventions, the method of spherical harmonic analysis, to the Earth's magnetic field to show that nearly all of it came from inside the Earth. He was also, with Humboldt, largely responsible for the 'Göttingen Magnetic Union', an international project for the simultaneous observation of the magnetic field on four selected term-days each year at a number of widespread sites. This scheme developed into the worldwide network of magnetic observatories that exists today. $\square$



Gauss's experiment. (a) The vibration experiment. The magnet, A, suspended by a silk thread, F, oscillates in a horizontal plane. Its moment of inertia can be varied by hanging weights, W, from the rod, R. The period of oscillation is obtained by observing the reflection of the scale, S, in mirror M, through the telescope, T, and timing an integral number of swings with the clock, C. (b) The deflection experiment. Magnet B is suspended and is deflected from magnetic north by placing magnet A at a known distance. The deflection is measured by observing the reflection of the scale, S, in mirror M, through the telescope, T.

S.R.C. Malin and D.R. Barraclough are in the Institute of Geological Sciences, Murchison House, West Mains Road, Edinburgh EH9 3LA.

Cause and treatment of atherosclerosis

from C.T. Dollery

The most common cause of death in developed countries is necrosis of heart muscle (myocardial infarction) resulting from obstruction of the arterial blood supply. The affected artery is usually narrowed by a plaque of atheroma. Two main hypotheses have been proposed for the origin of the atheroma, and although they are not mutually exclusive, as became clear at a recent symposium*, each tends to have its particular supporters.

The first hypothesis holds that plasma lipids diffuse into and are deposited in the arterial wall, and receives support from epidemiological evidence that relates levels of blood lipids in younger people to incidence of atheroma. The second hypothesis is that focal damage to the endothelium leads to deposition of platelets from the blood, release of platelet-derived growth factor and stimulation of smooth muscle migration and hypertrophy. The laminated appearance of many atheromatous deposits, suggesting successive deposition of thrombus, and the presence of platelet antigens in the plaques provide supporting evidence.

In plasma, lipid particles consist of a core of neutral lipid surrounded by protein (the apolipoprotein). A.M. Gotto (Baylor College of Medicine) likened the apolipoprotein to a detergent that solubilizes the lipid and put forward the 'iconoclastic' opinion that the apolipoproteins are more important than the lipids in understanding lipid transport and metabolism.

There are five classes of apolipoprotein (A-E) and many subclasses, and the apolipoproteins E have recently been sequenced. When the arginine residue is replaced at position 112 in apolipoprotein E₃, the molecule is not recognized by the lipoprotein E receptor. Homozygous inheritance of this E₃ deficiency can lead to type 3 hyperlipidaemia.

Lipoprotein receptors on cell membranes regulate entry of lipids into cells, are a target for specific lipoproteins and regulate the plasma lipoprotein concentrations. The best studied lipoprotein receptor is the low-density lipoprotein (LDL) receptor whose absence is responsible for familial hypercholesterolaemia. T.P. Bersot (University of California, San Francisco) showed that this receptor interacts with apolipoproteins B and E (Apo-B is the main apolipoprotein found in LDL whereas E is found in very low-density and high-density lipoproteins). The Apo-B/E receptor has a molecular weight of about 106,000, requires the presence of divalent cations and is inactivated by pronase.

A key difficulty in clinical research is assessing the amount of atheroma in a living human artery. D.H. Blankenhorn (University of Southern California) is using angiograms of the femoral and coronary arteries and computer image processing techniques. The centre line of the vessel is established and variations of wall distance at multiple transverse sections measured. The method has proved successful in postmortem material and is now being used *in vitro* to assess response to lipid-lowering agents. He was hopeful that the method could be applied to intravenous, rather than arterial, injections of radiographic contrast material to permit more frequent measurements. Radiological methods may be replaced by ultrasound in the not so distant future.

Lipid-lowering drugs (clofibrate, cholestyramine, nicotinic acid) have been found to be almost uniformly ineffective in reducing myocardial infarction mortality. In the WHO-sponsored clofibrate trial coordinated by M. Oliver (University of Edinburgh), there had been a reduction in non-fatal myocardial infarcts (none in fatal ones) but the overall mortality had been significantly greater in the treated group. The most effective anti-thrombotic drugs so far used had been the coumarin anticoagulants which had reduced mortality by about 20 per cent compared with placebo. Anticoagulants were almost discarded in the UK in the early 1970s but use has continued in the Netherlands (A.S. Douglas, University of Aberdeen). A recent randomized trial of withdrawal of long-term anticoagulant therapy in that country showed a higher mortality in those who stopped therapy than in those who continued therapy. Trials with anti-platelet drugs (aspirin, dipyridamole, sulphinpyrazone) had shown a smaller effect. The largest trial with aspirin had shown no benefit and the interpretation of one of the sulphinpyrazone trials was hotly contested. Overall these drugs had reduced myocardial infarction mortality by about 10–15 per cent. Four recent positive trials with β -adrenergic blockade, which had shown a reduction of 25–33 per cent in mortality during the first three years after a myocardial infarct, were mentioned only briefly. The speakers would not be drawn into a discussion of why myocardial infarction mortality has declined substantially in the USA but only very slightly in the UK. When asked whether we should all start jogging, restrict saturated fat intake, stop smoking and treat mild hypertension (or await better evidence of efficacy), one of the Americans said that we probably should, and quoted Irvine Page's aphorism "I don't want to be the smartest man in the graveyard".

The last session was concerned with

platelet function and the role of prostaglandins in vascular disease. Platelet plugs form very rapidly when small vessels are ruptured and platelet adhesion and aggregation is usually the first step in arterial thrombosis. At least three different mechanisms are responsible for platelet aggregation — contact with collagen, release of ADP and release of the arachidonic acid endoperoxide product thromboxane A₂ (TXA₂). TXA₂, released from platelets and damaged tissues, has received much attention recently but G. Born (King's College, London) reported experiments on bleeding time from punctures made in small mesenteric vessels which support a major role for ADP. The question is important as great efforts are being made to develop inhibitors or antagonists of TXA₂.

PGI₂ (prostacyclin) has attracted great interest because it is formed by the endothelium of blood vessels and is a powerful inhibitor of platelet aggregation. S. Moncada (Wellcome Research Laboratories) suggested that its physiological role is to prevent interactions between platelets and the blood vessel wall. PGI₂ interacts with a receptor on platelets which raises the level of cyclic AMP, makes them less aggregable and inhibits the exposure of fibrinogen receptors on their surface. Moncada was optimistic of the usefulness of PGI₂ in preventing clotting in extracorporeal circulations (cardiopulmonary bypass, charcoal column haemoperfusion, renal dialysis), in platelet consumption coagulopathies (haemolytic uraemic syndrome) and in peripheral vascular disease (gangrene of the lower extremities, Raynauds phenomenon). Others agreed about the value of PGI₂ as a heparin-sparing agent in extracorporeal circulations but contested its value in peripheral vascular disease.

C.T. Dollery (Royal Postgraduate Medical School, London) described a new method for measuring plasma 6-oxo-PGF, the hydrolysis product of PGI₂, which uses gas chromatography-negative ion chemical ionization mass spectrometry and has a sensitivity limit of 500 pg ml⁻¹. The concentrations he measured in venepuncture samples from normal humans were very low, averaging 1.2 pg ml⁻¹, and were almost certainly too low for PGI₂ to have a physiological role in the normal circulation. Large amounts of PGI₂ produced by isolated tissues and perfused organs are caused by the injury involved in their preparation. However, PGI₂ was released in substantial quantities *in vivo* as a result of trauma caused by passing vascular catheters in man or dog and by infusions of hypertonic dextrose into a human forearm vein. He proposed that PGI₂ released from damaged endothelial cells prevented the propagation of the luminal face of a platelet clot in a punctured vessel and inhibited

*The Biological Council symposium on 'Atherosclerosis: Mechanisms and Approaches to Therapy' was held at the Imperial College of Science and Technology, London, on 5–6 April 1982.

C.T. Dollery is Professor at the Royal Postgraduate Medical School, Duane Road, London W12 0HS.

platelet aggregation in a vessel that had been damaged but not severed. Possible application of this theory to atheroma depended on the frequency and importance of focal damage to arterial endothelium *in vivo*.

The symposium left mixed impressions. Animal and human studies on the pathogenesis of atheroma seem to be making only slow progress. Much of the difficulty arises from the unsatisfactory nature of the animal models and the difficulty of studying a process in man which progresses over decades. In contrast, lipid biochemistry and pharmacology are making important discoveries and eventually this basic knowledge should yield dividends in new forms of therapy. The problem is when, as there appears to be nothing of great promise on

the immediate horizon. New methods of measuring plaque regression will make early human studies feasible but very prolonged outcome trials will still be needed. The general gloom about the immediate prospects for development of therapeutic agents can be summed up by two quotes from the discussion "May the risk of controlling risk be greater than the risk itself?" and "You can be sure that a new treatment will do someone harm. You cannot be sure, until you do a large-scale clinical trial, that it will do anyone any good". Your correspondent was excited by the new developments in biochemistry and pharmacology of both the lipoproteins in the blood and the fatty acids in cell membranes and hopes these pessimistic views are wrong. □

The nuclear pore — a biological grommet?

from N. Michael Green

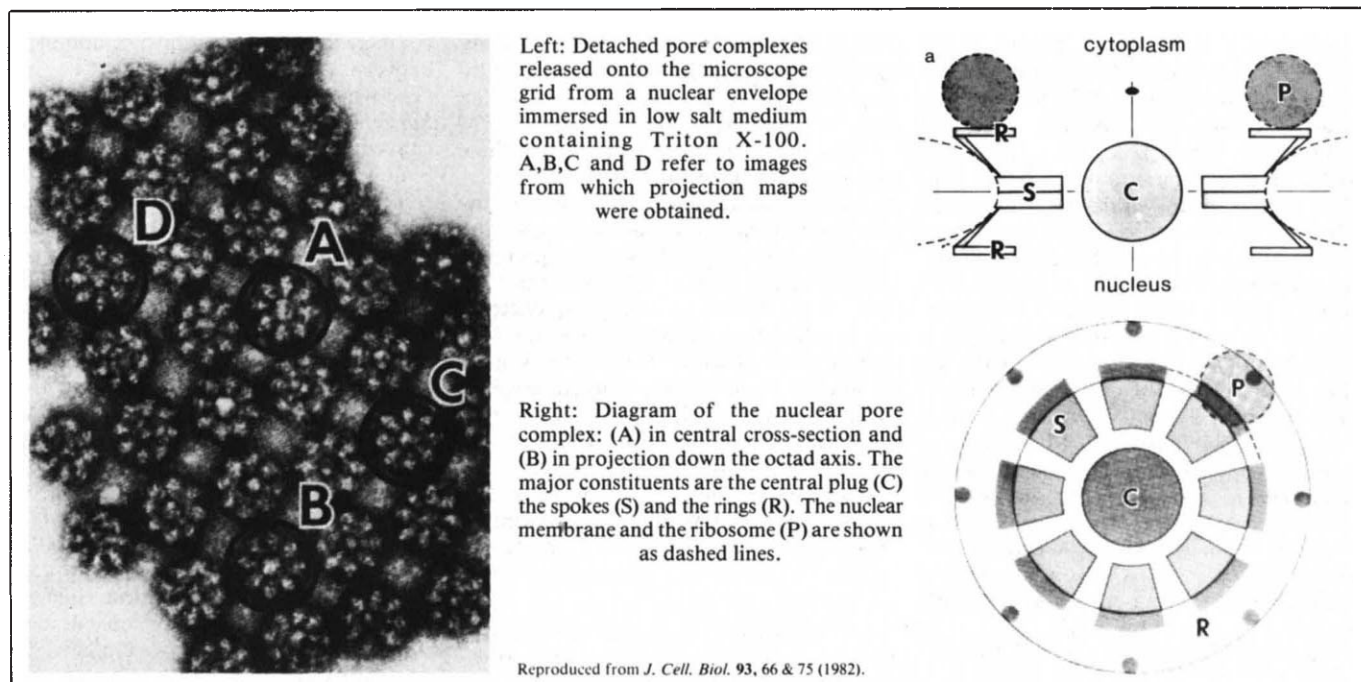
THE double membrane surrounding the nucleus is penetrated by nuclear pore complexes, recognized from the early days of electron microscopy as large structures (1,200 Å in diameter) with a striking eightfold rotational symmetry (reviewed by J.R. Harris in *Electron Microscopy of Proteins* Vol. 1, Academic, New York, 1981). Although they are referred to as pores, the channel is usually filled with a dense plug. The general features of the complex have long been recognized but higher resolution has been prevented by the lability of the structure, which is readily distorted by the processing required

for microscopy. New information has now emerged in a paper by Unwin and Milligan (*J. Cell Biol.* 93, 63; 1982). They used the favoured nuclear envelope of the *Xenopus* oocyte, which contains such a high density of pores that they tend to form tetragonal arrays. The topology of such an array is similar to that of the intercellular gap junction, but whereas the latter shows a regular lattice stabilized by protein interactions, the pores in the nuclear envelope remain distinct and appear to have rotational freedom in the paired lipid bilayers. Nevertheless, the close packing provides mutual support and minimizes distortion caused by drying in the negative stain (either uranyl acetate or gold thioglucose).

The most revealing pictures were obtained by allowing the nuclear envelope to adhere to hydrophilic, polylysine-treated carbon film and then washing either with high salt or with 0.1 per cent Triton X-100. This released both the intact complexes and various substructures, which adhered to the film in the neighbourhood of the original envelope. The following constituents were observed: (1) low-contrast rings with an internal diameter of 800 Å and an external diameter of 1,200 Å; (2) a dense central plug of diameter 370 Å; (3) eight particles of diameter 220 Å, possibly ribosomes, bound to the rings, enhancing their eightfold symmetry, and (4) broad radial spokes which in some way link the plug to the rings. Deciphering the three-dimensional organization of these components was greatly aided by occasional oblique and edgewise views of the complex, from which maximum information was obtained by examining the specimen at various angles on the tilting stage. Individual images, edgewise or *en face*, were analysed by numerical Fourier methods to give an accurate radial density distribution and an approximate distribution perpendicular to the membrane.

Because of the restriction to single images, rather than a regular array, and the problems of specimen preservation, the resolution was limited to 90 Å. Nevertheless, a fascinating picture emerges. The pore structure is basically a three-layered sandwich of a disk between two thin rings. The disk, consisting of a central plug and eight broad spokes, is suspended between the rings by slender extensions of the spokes. Each ring is coplanar with one half of the double membrane. Within the outer circumference of each ring the membranes approach each other, following the

N. Michael Green is in the National Institute for Medical Research, Mill Hill, London NW7 1AA.



direction of the connecting strands until they fuse in the mid-line around the periphery of the spokes, at a diameter of 1,000 Å. This interpretation of the structure implies that there are no transmembrane proteins in the usual sense; the proteins of the pore complex merely provide a grommet which stabilizes the hole formed by local fusion of the paired membranes. The eight 'ribosomal' particles were attached only to the cytoplasmic face of the grommet. These particles were readily removable by high salt or EDTA, leaving a structure which at this resolution had eight twofold symmetry axes at right angles to the main eightfold axis.

These findings provoke many further questions about both the structure and function of the pore complex. It has long been known that the nuclear membrane is freely permeable to ions and small metabolites and that even molecules as large as about 90 Å in diameter can pass across with little hindrance. This is consistent with the structure proposed by Unwin and Milligan, but it is less easy to see how ribosomal particles (200 Å in diameter), assembled in the nucleus, manage to pass through the pore. It is possible that this process may be energy

dependent and that some movement of plug or spokes is involved. Further structural questions concern the proteins which form the pore structure. Earlier work by Krohne, Franke and Scheer (*Expl Cell Res.* **116**, 85; 1978) has shown only two major components (MW 73,000 to 150,000) in purified pore complexes, together with several minor components. It should be possible to determine the location of at least the major constituents by immunological methods. Beyond this there is the problem of how the assembly of such large structures is controlled. From the dimensions it can be calculated that each of the major constituents (plugs, rings and spoke assembly) must contain several hundred molecules of their constituent protein subunits, giving them 'molecular weights' of 20–40 million. There is no way in which so many identical building blocks will assemble spontaneously into a precise limited structure without some guiding activity by the minor protein constituents or other cellular components.

These provocative developments provide an interesting example of the information which can be extracted from electron micrographs by modern image processing methods, even in the absence of extensive repeating structures. □

fibres are made but not those corresponding to S and U.

The recombinational control which underlies the three examples mentioned above and is exemplified by the variation in host range of Mu is fundamentally different from control of protein synthesis by positive and negative feedback circuits. Such circuits are able to modulate the activity of genes and, in the extreme case, turn them off completely. Recombinational control, on the other hand, introduces a two-way switch into these circuits, allowing alternative pathways to be introduced into the system. This added flexibility is useful when only one of two possible phenotypes can be tolerated at a particular time. It is well known from experiments involving mixed infection of cells with wild-type phage and host-range phage mutants that progeny particles which receive a mixed complement of tail fibres acquired from different parents have the worst of all worlds, not being able to adsorb properly to any of the usual hosts. If the host range of a phage, such as Mu, is to be extended by providing two distinct sets of tail fibres, then it is clearly advantageous that only one set or the other should be synthesized at any stage — a two-way switch is therefore appropriate.

The precise recombinational mechanism by which the switch between mating types is instituted in yeast, where some type of gene conversion seems to occur, is different from the inversion systems used to bring about phase variation in *Salmonella* or the alternation in host range shown by Mu (and also by phage P where a closely related system operates). All these inversion switches use site-specific recombination systems which act on the short inverted repeats at either end of the relevant inverted region, and which are catalysed by genes immediately adjacent to it. Surprisingly, although the invertible regions in *Salmonella* and Mu are quite distinct, there is some sequence homology between their inverted repeats. The *gin* gene which mediates G inversion and the *hin* gene mediating inversion in *Salmonella* can complement each other (Szekely & Simon *J. Bact.* **148**, 829; 1981). The known recombinational switches of the inversion type therefore all seem to stem from some common origin. Another evolutionary oddity of the G system is that the emergence of two kinds of Mu phage with different host ranges would be expected to lead to an increase in the number of bacterial strains which harbour Mu prophage. However only the original Mu isolate detected in *E. coli* K12 has ever been reported. Whatever the reason for this, the whole of the G region has been preserved in the Mu phage we have, even though within K12 strains part of the region (and the *gin* gene) could easily be deleted and the phage locked in the (+) orientation. Perhaps there is still another twist to come in the G story by which G and *gin* are implicated in some other aspect of the Mu life cycle. □

A novel gene splice in phage Mu

from Neville Symonds

GENE expression is usually thought of as being controlled through the action of proteins, such as repressors and effectors. Recently, a different mode of control has been reported whereby inactive genes are relocated by some type of recombination process to new sites where transcription takes place. Examples of recombinational control are mating type in yeast (Leupold *Nature* **283**, 811; 1980), phase variation in *Salmonella* (Zieg & Simon *Proc. natn. Acad. Sci. U.S.A.* **77**, 4196; 1980) and host range in phage Mu (Van de Putte *et al.* *Nature* **286**, 218; 1980). The last example refers to the unexpected finding that two types of Mu phage can be detected which differ with regard to the bacteria they can infect. The difference in host specificity is correlated with the two possible orientations observed in the G region of Mu, an invertible segment of about 3,000 base pairs. With G in one orientation, designated (+), Mu phage can adsorb to one set of hosts, which includes *Escherichia coli* K12; in the other orientation, (–), the phage adsorb to a different set, including certain *Citrobacter* and *Shigella* strains. How does the oscillation in G orientation bring about alterations in host specificity?

In general terms the answer to this question has been known for some time.

With G in the (+) orientation, two Mu genes, S and U, which code for tail fibres and enable the phage to adsorb to certain hosts, are expressed; in the (–) orientation two alternative genes, S' and U', are expressed, so the host range is altered. The actual genetic mechanism by which this switch is accomplished has, however, only now been elucidated and is described by Giphart-Gassler and co-workers in this issue of *Nature* (p.339).

The intriguing point to the story is that, in a manner somewhat reminiscent of that used to create diversity among immunoglobulins, the variation between the S and S' genes is brought about by joining a constant DNA sequence, S_c, adjacent to G with either of two different sequences S_v or S_v' located within G. In the (+) orientation, transcription starts at a promoter site outside G, proceeds through S_c and S_v, and then through the adjacent U gene which lies wholly within G. Tail fibres corresponding to S and U are therefore produced. In the (–) orientation the situation is reversed, the reading being in the order S_c + S_v', U', so that S' and U' tail

Neville Symonds is Professor of Microbial Genetics in the School of Biological Sciences, University of Sussex, Brighton BN1 9QG.

REVIEW ARTICLE

Active chromatin

Stuart Weisbrod

Cold Spring Harbor Laboratory, PO Box 100, Cold Spring Harbor, New York 11724, USA

Active genes are packaged into an altered nucleosome structure forming a chromosomal domain defined by increased sensitivity to nucleases. This structure, reflecting a potential for transcription, contains sites hypersensitive to nuclease digestion adjacent to the coding regions and may also be distinguished by specific non-histone proteins, variant or modified histones or modified DNA. Its formation, by unfolding of a tightly packed chromatin fibre by factors which might affect DNA supercoiling, may be the first step in gene activation.

REGULATION of gene expression is a fundamental mechanism in eukaryotic development and survival. The structure of the chromosome is directly related to this regulation since, for the most part, the DNA in the nucleus is compacted too tightly to be available to the transcriptional apparatus. Therefore the chromatin structure of genes which are transcribed, approximately 10–20% of the total, has to be different from that of the bulk of the DNA. Both the 'housekeeping' genes, those which are expressed in all cell types in the organism, and the genes which distinguish one cell type from another, exist in the active conformation.

Studies on eukaryotic chromosomes have focused mainly on the basic unit of chromatin, the nucleosome, and on how the individual nucleosomes are packed together. The existence, structure, and packaging of nucleosomes have been the subject of a number of reviews^{1–3}. Most of the evidence in these studies stems from electron microscopy, where a beaded chromatin fibre is observed, and enzymatic studies which reveal the existence of a repeating unit. The nucleosome consists of 146 to 240 base pairs of DNA wrapped twice around a histone core, made up of two each of the four inner histones H2A, H2B, H3 and H4. A fifth histone, H1, is also associated with the nucleosome but in a manner which is not clear. Extensive endonuclease digestion of chromatin produces a nucleosome core particle containing 146 base pairs of DNA and the histone core (but not H1), indicating that the heterogeneity of nucleosome DNA length is due to variability in the length of DNA linking one nucleosome to the next. The digestion studies also suggest that histone H1 is associated with this 'linker' DNA.

The nucleosome is also involved in the higher orders of structure that fold the DNA into the compact form found in the nucleus. The basic level of organization is the 100 Å 'beads-on-a-string' fibre generated by folding of the internucleosomal linker DNA⁴. This fibre is then coiled into a 300 Å fibre, possibly induced by histone H1 as a crosslinker, to yield a structure with a packing ratio of 25:1, close to that of interphase chromatin⁵. To make a mitotic chromosome from the 300 Å fibre a further two orders of magnitude of compaction are generated by specific nonhistone proteins which form the skeleton or scaffold of the chromosome⁶. Electron microscopy of histone-depleted metaphase chromosomes has demonstrated that the DNA is organized in loops at least 30–40 kilobases in length. Each loop of the chromatin is attached to the scaffold at its base, either by DNA-protein or DNA-RNA interactions⁷, and may exist in an expanded or a highly compacted conformation.

A nucleosomal repeat structure does not distinguish between inactive and active genes. Thus the DNA sequence complexity of mononucleosomes is virtually indistinguishable from that of total DNA and they contain sequences corresponding to transcriptionally active genes⁸. The nucleosome structure of active

genes has also been demonstrated by immuno-electron microscopy⁹. However, there are many ways in which the structure of chromatin from actively transcribed genes could or does differ from that of non-transcribed regions; what is known of these differences will be summarized here.

Nuclease digestion studies

Evidence that chromatin from actively transcribed genes exhibits a structure different from that of non-transcribed regions stems from the use of relatively nonspecific endonucleases as probes in anticipation that they would recognize something special about active genes. Weintraub and Groudine¹⁰ have shown that the globin gene in chick erythrocyte nuclei is preferentially sensitive to digestion by pancreatic DNase I, but not to digestion by micrococcal nuclease. The resistance of the globin gene to micrococcal nuclease suggests that the globin gene is packaged into nucleosome-like particles; its sensitivity to DNase I indicates that these particles are conformationally different from most nucleosomes. The sensitivity of the globin gene to DNase I is tissue specific. Globin chromatin is preferentially digested in red blood cells, but not in the oviduct; conversely, the ovalbumin gene is preferentially sensitive in the chick oviduct but not in red blood cells¹¹.

The sensitivity to DNase I of actively transcribed genes seems to be a general phenomenon^{12–15}, but only reflects a potential for a gene to be transcribed rather than transcription itself. For example, the ovalbumin gene remains sensitive in the hormone-withdrawn chick oviduct¹⁶, *Physarum* ribosomal DNA remains sensitive during mitosis when ribosomal RNA transcription is not detectable¹² and the mouse globin gene exhibits the same sensitivity in induced (transcribed) as well as uninduced (non-transcribed) Friend erythroleukaemia cells¹⁷. The boundaries of the sensitive regions of chromatin are very precise, since in a hamster cell line transformed by adenovirus, only those adenovirus sequences that are transcribed are sensitive to DNase I while adjacent non-transcribed sequences are not sensitive¹³.

Using DNase II, an enzyme which cuts primarily between nucleosomes, Gottesfeld and Butler¹⁸ have shown that after chromatin is digested, nontranscribed nucleosomes can be selectively precipitated with 2 mM Mg²⁺. The DNA in the active, non-precipitated nucleosomes is enriched for sequences coding for messenger RNA. Surprisingly, the active nucleosomes sedimented at 14S compared with 11S for bulk nucleosomes. When treated with RNase, the 14S structure converts to 11S, suggesting that the difference in S values can be attributed to the presence of nascent RNA chains. Other evidence¹⁹ confirms that this technique, as well as similar fractionation techniques using micrococcal nuclease²⁰, will only separate actively transcribing genes and genes which are

transcribed at different rates might be represented in different proportions in the active fraction. Since these procedures do not result in the complete digestion of active sequences, they are potentially useful for investigating the properties of active nucleosomes, but unfortunately they have proven difficult to reproduce.

Endonucleases have also been used to investigate higher order organization of active chromatin. A very light digestion of *Drosophila* nuclei by DNase I or micrococcal nuclease revealed preferential cleavage sites in a number of heat shock loci²⁰. These hypersensitive sites were originally suggested to act as boundaries of a supranucleosomal structure, but subsequent analyses (see below) have placed them within the active domain. The overall sensitivity of specific genes and adjacent noncoding regions has been measured by monitoring the disappearance of specific restriction bands after a mild DNase I digestion of nuclei²²⁻²⁴. In one case²³, a 25 to 50 kilobase region adjacent to the highly DNase I-sensitive globin coding region in erythrocytes was characterized, distinguished by a level of DNase I sensitivity intermediate between that of an expressed and a totally inactive gene. It was postulated that this domain might be equivalent to a lampbrush loop, and the DNase I sensitivity an indication that it is in a relaxed rather than a condensed configuration.

Proteins associated with active chromatin

Once the nuclease digestion experiments had demonstrated that the conformation of active nucleosomes is different from that of bulk nucleosomes, it was logical to seek the structural basis of this difference. From monitoring the proteins released by DNase I digestion and the characteristics of the various enriched fractions the suggestion arose that the active structure is due to altered or modified histones and/or the presence of nonhistone chromatin proteins in the nucleosome.

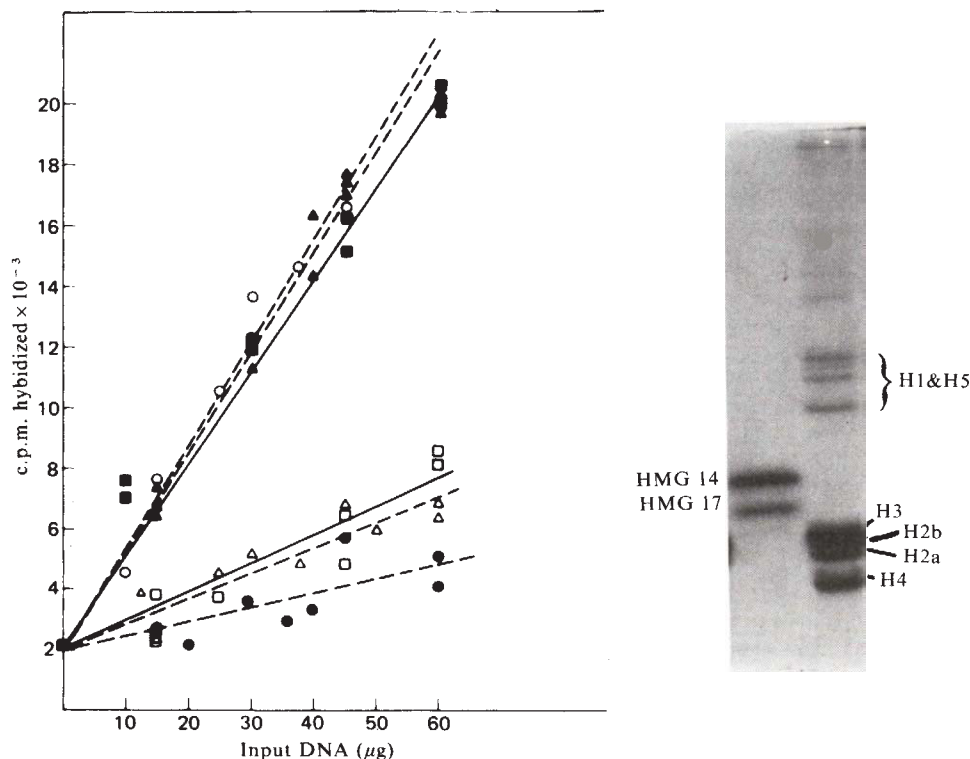
The nonhistone protein fraction most often detected associated with active nucleosomes is that of the high mobility group (HMG). The characteristics of this group have recently been extensively reviewed²⁵. HMGs are highly conserved proteins with low molecular weight (<30,000), have an unusual amino

acid composition containing approximately 25% basic and 30% acidic residues, and are easily eluted from chromatin in 0.35 M NaCl. They are present in amounts only approximately 5% of the nuclear DNA content and in, at most, 10–20% of the nucleosomes. They have been divided into two groups based on their solubility properties in trichloroacetic acid (TCA). HMGs 1 and 2 are soluble in 2% TCA but insoluble in 10% TCA; HMGs 14 and 17 are soluble in 10% TCA but insoluble in 20% TCA. The presence of HMGs in isolated mononucleosomes has been demonstrated by several biochemical means²⁶⁻²⁸. Furthermore, by the use of fluorescent antibodies, HMG-like proteins have been shown specifically to be associated with the transcriptionally active puffs in salivary gland polytene chromosomes²⁹.

Mononucleosomes enriched in nonhistone proteins have been prepared by limited digestion of nuclei with micrococcal nuclease³⁰⁻³². Levy-Wilson and her co-workers³², for example, have shown that a fraction enriched in active sequences, prepared by mild micrococcal nuclease digestion of trout testes nuclei and 0.1 M NaCl solubilization, is enriched in HMG T (analogous to HMGs 1 and 2), H6 (analogous to HMGs 14 and 17) and ubiquitin, and is depleted in histone H1. Analyses of these HMG-containing nucleosomes suggested that H6 was preferentially bound to the histone core while HMG T was associated with the internucleosomal linker DNA.

HMGs 14 and 17 can be eluted from chick erythrocyte chromatin with 0.35 M NaCl without any detectable change in the gross structure of individual nucleosomes; however, in this depleted chromatin the globin gene is no longer preferentially sensitive to digestion by DNase I³³. Reconstitution of the depleted chromatin with either the entire 0.35 M NaCl fraction or purified HMGs 14 and 17 at a ratio of 1 mole HMG per 10 moles of nucleosomes results in the successful reconstitution of DNase I sensitivity on the globin gene (Fig. 1)³³. Further reconstitution studies³⁴ have led to the following conclusions: (1) There is no tissue specificity associated with the HMGs; thus, HMGs 14 and 17 from brain nuclei are capable of restoring DNase I sensitivity to the globin gene when reconstituted with depleted red blood cell chromatin. (2) Most actively transcribed

Fig. 1 Reconstitution of DNase I sensitivity of the globin gene in 14-day-old chick embryo red blood cells with 10% TCA-soluble HMG proteins. Chromatin was eluted with 0.35 M NaCl and separated into several portions. One portion was reconstituted with the 0.35 M NaCl eluate directly (∇); a second portion was reconstituted with 10% TCA-soluble fraction from the 0.35 M NaCl eluate containing mainly HMGs 14 and 17 ($\square$); a third portion was reconstituted with the 0.35 M NaCl eluate previously treated with trypsin and then trypsin inhibitor ($\circ$); and a fourth portion was digested directly ($\blacktriangledown$). Each portion was then treated with DNase I so that 10–15% of the DNA was rendered acid soluble. The DNA was then purified and hybridized to an excess of globin cDNA. As controls, nuclei treated to 35% acid solubility with micrococcal nuclease ($\blacksquare$) showed no preferential digestion, whereas nuclei treated to 10% acid solubility with DNase I ($\bullet$) showed a significant loss of globin sequences. Reconstitution with 0.35 M NaCl alone or with neutralized and dialysed 10% TCA alone was unsuccessful in restoring DNase sensitivity (not shown). Input globin cDNA was 100,000 c.p.m. Also shown in an 18% SDS-polyacrylamide gel of total nuclear proteins and purified HMG 14 and 17 (from ref. 33).



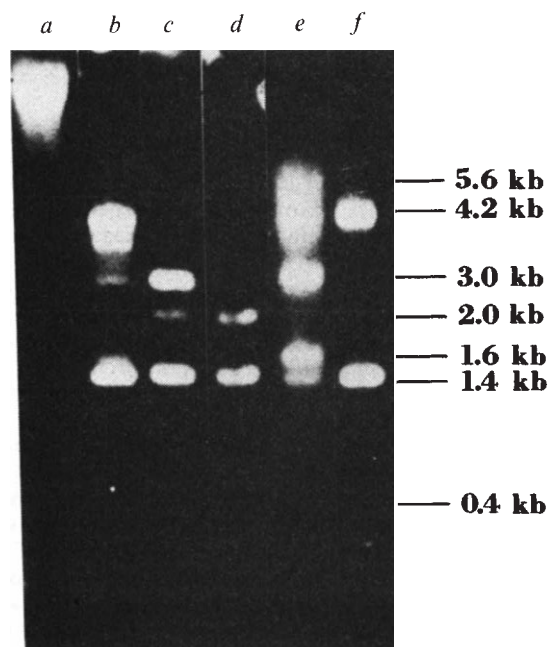


Fig. 2 The chicken adult β -globin gene is more methylated in 5-day embryos making embryonic haemoglobin than in 14-day embryos making adult haemoglobin. *a-d*, Partial digestion of adult erythrocyte DNA with *MspI*; *a*, no enzyme control; *b*, 2 units; *c*, 12 units; *d*, 100 units of enzyme; *e*, complete *HpaII* digest of 5-day erythrocyte DNA; *f*, complete digest of 14-day erythrocyte DNA. The DNA was electrophoresed on a 1% agarose gel. Southern blotted⁸⁰ and hybridized to an adult-specific β -globin probe, pHb1001. (From ref. 68.)

genes become sensitized to DNase I by HMGs 14 and 17. (3) Specificity for HMG binding seems to be in the recipient NaCl-depleted chromatin; thus, HMGs 14 and 17 from red blood cell chromatin fail to induce DNase I sensitivity to the globin gene when reconstituted with HMG-depleted chromatin from brain. (4) Either HMG 14 or HMG 17 can sensitize most actively transcribed genes to DNase I. (5) Genes transcribed at different rates have about the same affinity for HMGs 14 and 17. (6) HMGs 14 and 17 bind stoichiometrically to actively transcribed nucleosomes. (7) HMGs 14 and 17 can restore DNase I sensitivity to HMG-depleted nucleosome core particles containing 145 base pairs of DNA. And (8) as judged by sensitivity to DNase I, actively transcribed nucleosomes become associated with HMGs 14 and 17 within 3 minutes after these genes are replicated³⁵.

Taking advantage of the specific binding properties of HMGs described, an active nucleosome affinity column has been prepared, by coupling chicken HMGs 14 and 17 to agarose or glass beads, and used to map the DNA regions surrounding the chicken α -globin genes for their capacity to bind to HMGs 14 and 17³⁶. The results indicated a direct correspondence between chromosomal regions which are capable of interacting with HMGs 14 and 17 and the regions which are highly sensitive to DNase I digestion. In contrast, the chromosomal regions of intermediate DNase I sensitivity which are adjacent to the highly sensitive regions did not bind HMGs 14 and 17.

The positioning of HMGs 14 and 17 in active nucleosomes has been investigated in a number of ways, both directly using nucleosomes enriched in active sequences, and indirectly by reconstitution. Electrophoretic studies^{27,28,37,38} have indicated that HMGs 14 and 17 bind to a particle containing 150–160 base pairs of DNA, possibly replacing histone H1 and leading to a more open chromatin fibre. In contrast, HMG 14 (17)–H1 cross-linked products have been obtained³⁹ and it has been shown that total chick erythrocyte nucleosomes containing H1 or H5 are still able to bind HMGs 14 and 17⁴⁰. This complication may be due to the ease with which H1 is displaced from mononucleosomes during preparation⁴¹. Mapping of DNase I

cutting sites and thermal denaturation studies in nucleosome cores compared with HMG–nucleosome core complexes have suggested that the major sites of interaction of HMGs are located near the ends of the nucleosome core DNA⁴⁰. Furthermore, the characterization of subnucleosome particles produced by extensive micrococcal nuclease digestion has suggested that the HMGs are (partly) associated with histone-free DNA⁴². Thus the general consensus is that HMGs 14 and 17 occupy two binding sites at each end of the nucleosome core and cover or interact with internucleosomal DNA.

Much less is known about other non-histone proteins associated with active chromatin. However, increasing attention is being paid to sequence-specific DNA binding proteins which might have as important a role in gene regulation in eukaryotes as they do in prokaryotes. For example, Engelke *et al.*⁴³ have isolated a protein of molecular weight 37,000, TFIIIA, from a *Xenopus* oocyte homogenate which binds to the intragenic control region of 5S DNA and appears to be required for transcription. Positive regulatory control has also recently been shown by the sequence-specific binding of the glucocorticoid–receptor complex to cloned fragments of murine mammary tumour virus DNA⁴⁴. Conversely, repressor–operator control is shown by polyoma T antigen, which represses the synthesis of its own mRNA and the adenovirus DNA binding protein,

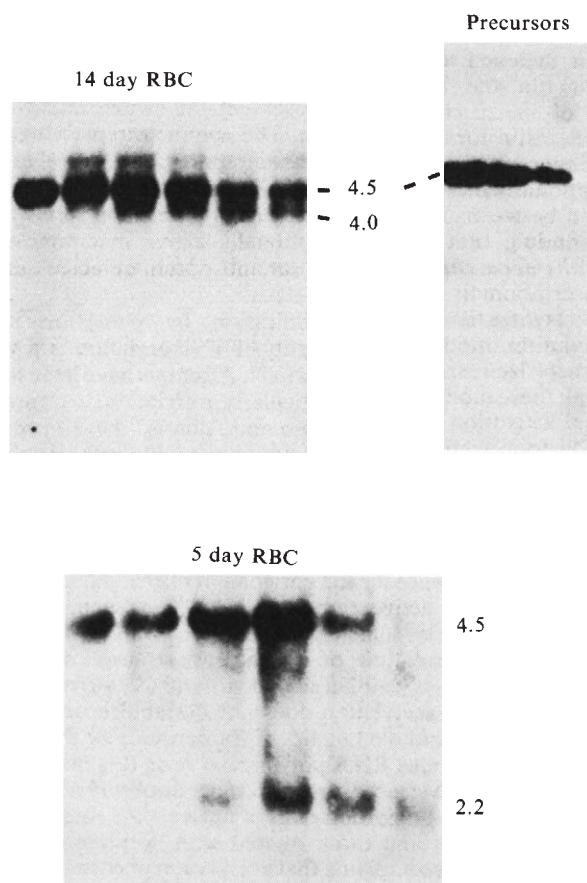


Fig. 3 Absence of DNase I-hypersensitive sites in globin chromatin from precursor cells. Nuclei from primitive erythroblasts (from 5-day embryos) making embryonic haemoglobin, definitive erythroblasts (from 14-day embryos) making adult haemoglobin, and precursor cells (500 embryos) were digested with increasing concentrations of DNase I. The DNA was purified, restricted with *HindIII* and blot-hybridized to an embryonic β -globin probe. Without DNase I digestion a 4.5 kilobase fragment is observed. In embryonic cells a discrete new band appears at 2.2 kilobases, whereas in adult cells the hypersensitive site disappears and a different region of hypersensitivity appears yielding a sub-fragment of about 4 kilobases. As a control the same precursor blot showed sub-bands after hybridization to a probe for the transcriptionally active actin gene. (From ref. 88.)

which represses the synthesis of adenovirus early region IV mRNA^{45,46}.

Modification of chromatin proteins

A fundamental manner in which chromatin conformation could be varied is by covalent modification of its histones or the DNA. Primary sequence variants of all five histones have been identified electrophoretically, especially with the use of Triton-acid-urea polyacrylamide gels⁴⁷. Species-specific, tissue-specific and gene-specific subfractions have been described⁴⁸. In most cases the role of histone variants in chromatin structure and function is unclear, but the occurrence of precisely timed staged-specific changes in histone subtypes during development^{49,50} suggests that they are important in differentiation.

Direct evidence for the specific exchange of one histone subtype for another has been obtained by analysing male pronuclear histones from polyspermically fertilized sea urchin eggs⁵¹. Between fertilization and morula the sperm-specific histones of every sperm nucleus are completely replaced by cleavage stage histones. Inhibition of protein synthesis by emetine indicated that the cleavage-stage histones are stored and are of material origins. The replacement of the individual histones does not occur coordinately. The switch in histone H1 occurs almost immediately while the core histones are replaced at specific intervals during the first eight divisions. Since histone H1 is believed to play a role in the higher order structure of chromatin, and the switch occurs before any gross decondensation of sperm chromatin is observed, the switch might be a prerequisite for nuclear fusion. The complete replacement of the inner histones might serve to derepress the relatively transcriptionally inert sperm genome. Further evidence for a correlation between histone subtypes and transcription stems from the finding that the transcriptionally active macronuclei of *Tetrahymena* contains several variants which are absent in the transcriptionally inert micronucleus⁵².

Postsynthetic histone modification by phosphorylation, acetylation, methylation and polyADP ribosylation is a well-characterized feature of chromatin⁵³. Attempts have been made to link these modifications, particularly acetylation, to transcriptional activation and Yamamoto and Alberts⁵⁴ have proposed that histone acetylation-deacetylation can provide the flexibility needed to transduce laterally across an active gene the increased accessibility to RNA polymerase. However, even though there are numerous correlations between an increase in histone acetylation and increased RNA synthesis (ref. 55 for example), and considerable evidence for the enrichment of acetylated histones in transcriptionally active chromatin^{18,36,56-60}, it seems unlikely that acetylation is sufficient either to produce an active chromatin conformation or to increase transcription rate. Studies of *in vitro*-assembled simian virus 40 (SV40) complexes have shown that acetylation does not destabilize or open up the nucleosome, and the kinetics of transcription of these complexes by calf thymus RNA polymerase A or B is not affected by acetylation⁵⁹. Moreover, no difference is observed on comparing the DNase I digestion rates of nucleosome core particles from control cells and those treated with butyrate to inhibit cellular deacetylase implying that acetylation of core histones is not necessary for DNase I sensitivity⁶¹. So although histone hyperacetylation is a characteristic of active genes, its function, if any, in transcription, is not known.

HMG proteins also undergo postsynthetic modifications⁶¹⁻⁶⁵. Recently, a careful analysis of the phosphorylation of HMGs 14 and 17 at different stages of the cell cycle in synchronized HeLa cells showed there to be a sevenfold increase in ³²P incorporation into HMG 14 in G₂ phase compared with G₁, and a twofold increase in incorporation into HMG 17 in early S phase⁶⁵. In contrast, HMGs 1 and 2 were not phosphorylated. Therefore, phosphorylation of HMG 14 may be a prerequisite for the events which follow G₂—that is, chromatin condensation and cytokinesis. Perhaps of greater significance was the finding that the stage-specific phosphorylation of HMG 14 parallels

that of histone H1, adding weight to the theory that HMGs 14 and 17 substitute for histone H1 in active regions.

DNA modification

The occurrence of a small fraction of modified bases in DNA has long been known (see ref. 66 for review). Over the past four years an inverse relationship has emerged between the presence of the most commonly modified base in eukaryotic DNA, 5-methylcytosine (m⁵C), and gene activation. Bird and Southern⁶⁷ have shown that some type-II restriction endonucleases, whose substrate contains the dinucleotide sequence CpG, could be used to probe for m⁵C by virtue of their inability to cut if the cytosine is methylated. Using these enzymes, specific sites have been shown to be undermethylated in the chicken β -globin gene in red blood cells (Fig. 2)⁶⁸, in the ovalbumin, ovotransferrin, and ovomucoid genes in the chicken oviduct⁶⁹, in amplified ribosomal genes in *Xenopus laevis*⁶⁷, in the human and rabbit globin genes^{70,71}, and in various integrated viral genes⁷²⁻⁷⁴. Furthermore, a direct correspondence between undermethylation, DNase I sensitivity and *in vivo* and *in vitro* transcription by endogenous RNA polymerase II has also been demonstrated⁷⁵. A caveat to all of these correlations, though, has to be made because there are many sites within active genes which remain methylated in all tissues and other sites which remain unmethylated⁶⁹.

If undermethylation were sufficient for gene activation, inhibition of methylation should result in the expression of otherwise repressed genes. When a mouse/human hybrid cell line is grown in media containing the cytidine analogue 5-azacytidine, which is incorporated into DNA but cannot be methylated (due to the replacement of carbon 5 with nitrogen in the pyridine ring) the inactive X chromosome is reactivated⁷⁶. Similarly, 5-azacytidine has been used to activate the metallothionein-1 gene in mouse lymphoid cells⁷⁷ and the endogenous retrovirus ev-1 in chicken lymphocytes⁷⁴. In both cases activation has been shown to be coincident with demethylation of specific *HpaII* sites in the coding regions of the respective gene. In the case of the retrovirus, the induction was also correlated to the acquisition of DNase I hypersensitive sites (see below) in both the 3' and 5' long terminal repeats. In contrast, the globin genes in the chicken lymphocytes are not

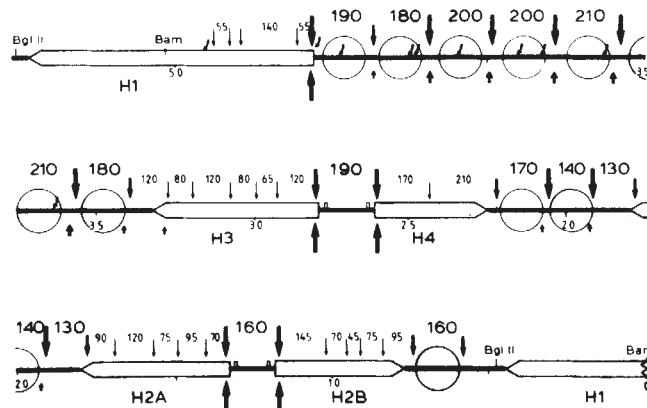


Fig. 4 Fine structure map of histone gene chromatin. Map of the 5.0 kilobase histone gene repeat, showing the transcribed regions as well as the direction of transcription for the five genes (large open rectangles with arrowheads). Numbers below the line, distance in kilobases from the *Bam*HI site on the extreme right. Small vertical rectangles above the line, TATA boxes. Arrows below the line, DNase I sites. Arrows above the line, micrococcal nuclease sites on the histone chromatin; the size of the arrows reflects the relative intensities of the corresponding bands on the autoradiograms. Curved arrows, micrococcal cleavage sites. Circles, static 146 base pair nucleosomes on the nontranscribed spacers. For clarity, 250 base pairs at the extreme left and right of the centre line are repeated on the upper and lower lines, respectively. (From ref. 84.)

activated by 5-azacytidine. Perhaps, then, the azacytidine-responsive genes are already distinct in some way from bulk chromatin. Supporting this is a finding that the inactive β -globin gene is about threefold less accessible to DNase I in *Xenopus* hepatocytes⁷⁸ than the inactive albumin gene is in erythrocytes or the vitellogenin gene is in either tissue. Therefore it seems that if demethylation is necessary for gene activation, it is not sufficient.

DNA of the transcriptionally active macronucleus of *Tetrahymena thermophila* is methylated at the N^6 position of adenine residues yielding N^6 -methyladenine (m^6A)⁷⁹. Approximately 1 in every 125 adenine residues is modified and there is no detectable m^5C . In contrast, the transcriptionally inert micronuclei contain m^5C and are devoid of m^6A . The m^6A -containing sequences are preferentially digested by both micrococcal nuclease and DNase I. Perhaps the function of these two types of modifications can be found in the differences in base pairing stability of the methylated and unmethylated pairs. The pair methyladenine-thymidine, characteristic of transcriptionally active regions, is more easily denatured than the non-methylated pair, while methylcytosine-guanine, characteristic of inactive regions, is more stable than the corresponding methylated pair.

Higher order chromatin structure

In addition to the high degree of DNase I sensitivity characteristic of active chromatin, there are also small regions of nuclease hypersensitivity, less than 200 base pairs, usually but not always 5' to the coding region. The double-stranded cuts can be mapped by mildly digesting chromatin with either DNase I or micrococcal nuclease, purifying the DNA, redigesting with a restriction endonuclease and probing, by Southern blotting⁸⁰ with a short ³²P-labelled DNA fragment which abuts the restriction cut. DNA fragments smaller than the expected mapped restriction bands appear, the length of which defines the distance between the restriction site and the DNase I cut. Using this indirect end-labelling technique, Wu has demonstrated the presence of hypersensitive sites 5' to the 70,000 and 83,000 molecular weight heat shock genes (*hsp* 70 and 83) in *Drosophila* embryos and tissue culture cells⁸¹. Since these sites do not exist on naked DNA, they must be a function of chromatin structure. After heat shock, the whole of the active *hsp* 70 coding sequence becomes sensitive to DNase I but to a magnitude less than the 5' sensitivity, which is still partially retained. DNase I hypersensitive sites have also been demonstrated for the four small heat-shock genes⁸², in the chick ovalbumin, conalbumin, globin and endogenous retroviral genes^{22-24,74,75}, in the rat preproinsulin gene⁸³, in the *Drosophila* histone gene repeat⁸⁴, and in the SV40 minichromosome⁸⁵⁻⁸⁷. In *Drosophila*, a pattern of micrococcal hypersensitive sites resembling that of DNase I was also observed. With both enzymes preferential cuts within the gene itself are seldom seen.

In an extensive set of experiments, the occurrence of DNase I hypersensitive sites has been correlated to β -globin gene activation in early chick development⁸⁸. A comparison was made between a highly enriched red blood cell precursor population isolated from 20-23-hour chicken blastoderms deficient in globin transcription, embryonic red blood cells from 5-day old chicken embryos which express the embryonic β -globin gene and adult red blood cells from 14-day-old chicken embryos which express the adult β -globin gene. Hybridization of an embryonic β -globin probe to a *Hind*III digest of DNase-treated nuclear DNA is shown in Fig. 4. No hypersensitive sites were observed in the red blood cell precursors, whereas the embryonic and adult cells both had hypersensitive sites but different ones. It should be noted that the change in chromatin structure from embryonic to adult red blood cells does not occur directly; rather, the stem cell chooses one of two directions. In these experiments transcriptional activity was further correlated to undermethylation. Since the two globin genes exhibit the intermediate level of DNase I sensitivity in both cell types, it is attempting to conclude that the presence or absence of a hyper-

sensitive site dictates which gene is transcribed. Other evidence suggests that this is not always true. The α and β major globin genes in murine erythroleukaemia cells show a high level of DNase I sensitivity and are transcribed at a low but detectable basal level. However, upon induction of globin synthesis with hexamethylene bisacetamide a new 5' DBase I hypersensitive site is generated⁸⁹. A possible problem with this result, however, is that the globin transcription detected before induction might only be occurring in a small subpopulation of cells.

Recent results have strongly suggested that the nuclease hypersensitivity of certain regions of chromatin is due to localized single-stranded regions of DNA in a nucleosome-free environment. Tissue-specific cleavages roughly corresponding to the known DNase I hypersensitive sites 5' to the chick globin genes have been observed using the single-strand specific nuclease *S*₁ (ref. 90). When DNA regions containing these sites are subcloned into the pBR322 plasmid the cleavage sites are retained if the plasmid is supercoiled but lost if it is linearized. This suggests that the strain of supercoiling induces a change in DNA conformation which is sequence-specific. This supercoiling stress might be mimicking the natural effect of an altered nucleosome conformation or a sequence-specific binding protein in chromatin. Furthermore, it has recently been shown²⁴ that the 5' hypersensitive site in the chick adult β -globin gene actually extends over 200 base pairs, 115 base pairs of which can be excised by *Msp*I digestion as protein-free DNA, suggesting the absence of a nucleosome.

DNA footprinting analysis of the interaction between the *lac* operator and repressor has shown that the binding domain of a protein can be 10- to 100-fold more sensitive to DNase I digestion when the protein is bound⁹¹. Therefore hypersensitive sites may represent regions of specific interaction with DNA sequence recognizing proteins. Consistent with this is the finding that the origin of replication and transcription of SV40 and polyoma which interacts with T antigen and the promoter region of the *Xenopus* 5S RNA genes which interact with TFIIA⁹²⁻⁹⁵ are preferentially nuclease sensitive. The presence of a specific DNA binding protein probably excludes nucleosome formation. Reconstitution studies⁹⁶ using calf thymus histones and *lac* operator DNA have indicated a preferred register of histones with respect to DNA sequence, demonstrating a further limit in the distribution of nucleosomes. Moreover, in the 250 Å chromatin fibre, the nucleosomes are arranged in a zig-zag fashion^{97,98}, the DNA in one nucleosome adjacent to the histones in the next enabling minor changes in position to be rapidly propagated along the fibre.

These studies have led to the postulate, and subsequent demonstration, that nucleosomes could be located in a unique or a small number of distinct positions relative to DNA sequence. This arrangement, termed phasing, has been the subject of two recent reviews^{99,100}. It has led to a disagreement (perhaps semantic) of whether phasing is the result or the cause of the binding of regulatory proteins with respect to DNA sequence. There has also been some concern that phasing was an artefact of the marked specificity of micrococcal nuclease for A + T-rich regions. However, in carefully controlled experiments using both micrococcal nuclease and DNase I, it has been shown, for example, that nucleosomes are precisely positioned on the nontranscribed spacer region in the *Drosophila* histone

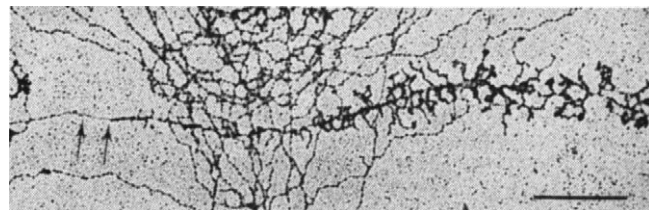


Fig. 5 Proximal portion of an active Balbiani ring transcription unit from the salivary glands of *Chironomus tentans* showing initial segment of unbeaded chromatin (arrows). Scale bar, 0.5 μ m. (From ref. 103.)

gene repeat (Fig. 5)⁸⁴. It was also shown that the nucleosome arrangement is established early in development and is retained throughout the remainder of the *Drosophila* life cycle.

Electron microscopic analysis

It is clear from the experiments described above that gene expression in eukaryotes is characterized by many levels of regulation. Most of the DNA in a nucleus, while packaged into nucleosomes, is further folded into an extremely compact and condensed higher order structure opaque to the transcriptional machinery. It might be that the features associated with active genes such as undermethylation, nuclease sensitivity, acetylation, HMGs 14 and 17 act coordinately to affect the degree in which individual genes are available to prokaryotic-type regulatory mechanisms. In the case of lampbrush and polytene chromosomes^{101,102}, gene activation is directly preceded by the chromatin fibre changing from a tightly packed state to a more open loop-like conformation. Specific active transcription units have been visualized for the Balbiani rings on chromosome IV in the salivary glands of *Chironomus tentans*¹⁰³ and on the ribosomal RNA genes in *Oncopeltus fuscatus* embryos¹⁰⁴ by an electron microscopy technique developed by Miller and Bakken¹⁰⁵.

Inactive chromatin exhibits a uniform beaded appearance in the electron microscope, while active transcription units are visualized as a gradient of ribonuclear protein fibres anchored to the base of the chromatin fibre by RNA polymerase molecules to yield the archetypical 'Christmas tree', the apex of which is coincident with the initiation of transcription. The Balbiani rings 1 and 2 transcription units generate 75S mRNAs coding for the salivary polypeptides. Careful measurement of the length of the transcribing chromatin has shown a marked extension of the fibre, the packing ratio going from 1.9 to 1.6 (defined as the length of B-structure DNA per unit length of chromatin)¹⁰³. Nucleosome-size beads were observed in the active transcription units but with a frequency decreased to 4 per μm from the 28 per μm found in inactive chromatin. Furthermore, there appeared to be a smooth nonbeaded segment, 0.18 μm or about 500 base pairs in length directly preceding the RNP fibre gradient (Fig. 5). This could correspond to a 5' DNase hypersensitive region (see above), though it could also be an artefact of unusual tension during the spreading procedures.

Structural changes in ribosomal DNA transcription units, which can be identified morphologically, have been studied during early development in *Oncopeltus*¹⁰⁴. At 32 hours after fertilization (late blastula) only beaded chromatin is seen, but 6 hours later, before ribosomal RNA synthesis is detected biochemically, nonbeaded stretches of ribosomal chromatin appear—many of them lacking transcripts. Again, there is a decrease in packing ratio in this case from 2.3 to 1.2. Importantly, the rDNA still exhibits a 200-base-pair repeat, though as transcriptional activity increases so does the accessibility to nucleases¹⁰⁶. This result eliminates the possibility that the presence of numerous RNA polymerase molecules are responsible for the change in chromosome structure and indicates that the major change actually precedes transcriptional activation. This could occur by decondensation of a domain of the chromosome, and may possibly be equivalent to the preactivation state described by Weintraub and his colleagues¹⁰⁷.

Gene activation

Irrespective of the many characteristics of active genes described here, transcriptional activation still relies on the initial decondensation of a domain of the chromosome containing the gene to be transcribed. Recently, two possibly inter-related phenomena have been described which may be involved in this event. The yeast *Saccharomyces cerevisiae* can exhibit a or α mating type depending on the position in the chromosome where the mating type genes are located. There are three possible loci or cassettes which the genes could occupy: MAT, which is transcriptionally active, and HML and HMR, which

a b c d

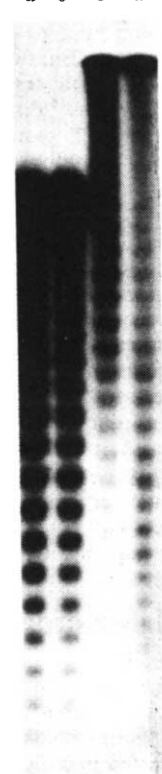


Fig. 6 Supercoiling difference in an active versus inactive yeast mating-type gene. A hybrid-yeast plasmid containing PBR, the centromeric region of chromosome 3, a selectable marker, Trp1, and either HML α or MAT α was transformed into a MAR⁺ or a MAR⁻ strain. The total DNA was purified and electrophoresed on a 0.7% agarose gel containing 2.5 $\mu\text{g ml}^{-1}$ chloroquine. The gel was Southern blotted⁹ and hybridized to pBR322. a, MAT α in MAR⁻ (K228 from A. Klar). b, MAT α in MAR⁺ (17-16 from A. Hopper). c, HML α in K228. d, HML α in 17-16. When the HML α gene is repressed in 17-16 it is more negatively supercoiled than when it is active in K228. The MAT gene functions independently of MAR. (From ref. 109.)

are repressed through the action of several unlinked genes equivalently termed MAR or SIR¹⁰⁸. When the cassettes are introduced into yeast on episomal plasmids by transformation they still exhibit normal regulatory control. Nasmyth and Abraham¹⁰⁹ have shown that the number of negative superhelical twists in a plasmid containing the HML locus is decreased when the plasmid is activated by being placed in a strain of yeast that is deficient in the MAR/SIR genes (Fig. 6). This raises the possibility that the MAR/SIR genes could function as type II topoisomerase molecules. Extrapolating back to the chromosome, decondensation could occur by the uncoiling of a 'lampbrush type' loop initiated by blocking of a sequence-or repertoire-specific topoisomerase.

Alternatively, decondensation/condensation may be associated with the formation of left-handed or Z-form DNA as occurs in the interband regions of *Drosophila* polytene chromosomes¹¹⁰. In physiological salt solutions Z-DNA is not stable and readily converts to the B conformation. It can be stabilized, however, by supercoiling, binding of specific basic proteins such as spermine and spermidine, or by the presence of 5-methylcytosine¹¹¹. Rich and his colleagues¹¹⁰ have proposed that selective demethylation of Z-DNA, thereby destabilizing it, would result in torsional stress. This stress can be overcome by positive supercoiling, which will result in an unwinding of the double helix at a position removed from the initial event, and yield a nuclease hypersensitive single-stranded region.

The primary events contributing to changes in higher order chromatin domains responsible for gene activation are just beginning to be investigated. Once known, secondary components directly involved in the act of transcription *per se*, such as the role of histone modification, HMGs and promoter/repressor control might be better understood. Only then may it become possible to answer some of the more fundamental questions of gene control and differentiation.

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ARTICLES

The range and unity of planetary circulations

Gareth P. Williams & J. Leith Holloway Jr

Geophysical Fluid Dynamics Laboratory/NOAA, Princeton University, Princeton, New Jersey 08540, USA

Altering the rotation rate, obliquity and diurnal period of an Earth-like model atmosphere produces a wide range of circulation forms, some of which resemble those observed on Venus, Mars, Jupiter, Saturn and (perhaps) on Uranus and Neptune. These unified solutions suggest: that Jupiter and Saturn resemble a larger, faster-spinning Earth and possess a stress-bearing or momentum-exchanging sublayer; that easterly winds prevail in Uranus' summer hemisphere; and that Venus resembles a slowly rotating Earth if diurnal heating variations are included.

FROM Venus to Neptune, the motions of the planetary winds are being explored and subjected to theoretical analysis and prediction. On Earth, Mars and Jupiter the winds appear to exhibit similar arrangements and to obey similar laws^{1–3}. These affinities stem mainly from the constraints placed on large-scale motion by planetary rotation^{4,5}. To learn more about the influence of rotation on the structure of the planetary winds

and to determine the range of circulation forms, we evaluate in this article the response of a representative (Earth-like) model atmosphere to changes in rotation rate, obliquity and diurnal period.

Our numerical experiments show that an Earth-like atmosphere, when placed in the rotational configuration of another planet, displays that planet's form of motion: Jupiter, Uranus

and Venus appear to behave like rapidly rotating, oblique and slowly rotating Earths, respectively—despite thermodynamical and other differences. This suggests that the basic meteorology of the Solar System is relatively simple, unified and Earth-like, even though more complex meteorologies are needed for understanding the finer details of individual planetary circulations. The solutions thus provide an elementary indication of

the dynamical laws and processes acting in the various planetary atmospheres.

Modelling

Our standard climate simulation model (GCM) integrates the equations of atmospheric motion, thermodynamics and conservation of mass and moisture in space and time, using spectral

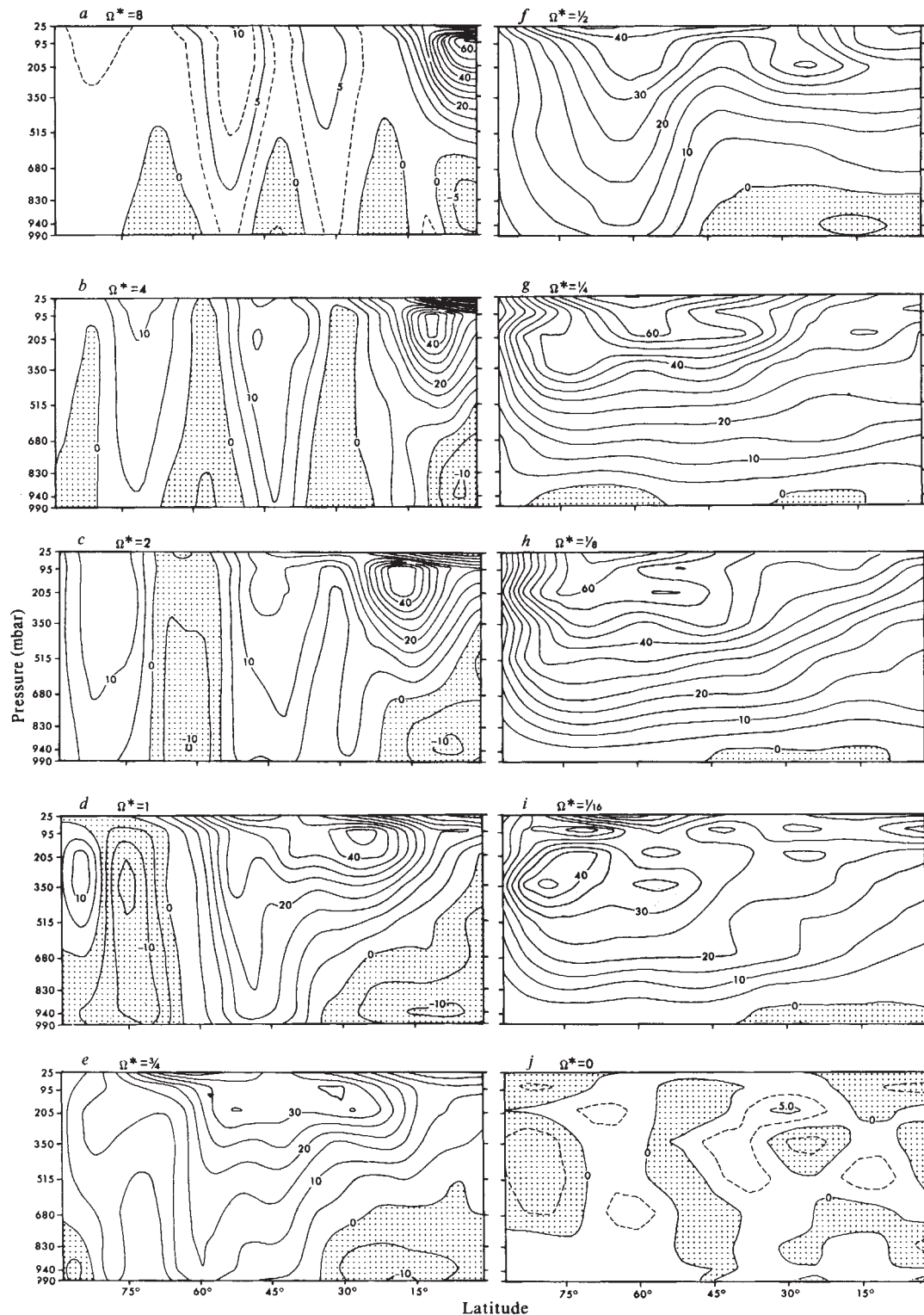


Fig. 1 The mean zonal flow of an Earth-like model atmosphere (subject to the annual-mean heating parameters) at different relative rotation rates, Ω^* . Similarities may exist between Jupiter, Saturn, Uranus, Neptune and *a-c*. Easterly winds are shaded; the main contour interval is 5 m s^{-1} and the supplementary one, 2.5 m s^{-1} . Pressure is used as the vertical coordinate. Calculations use a hemispheric sector, 120° in longitude, and horizontal rhomboidal spectral resolutions of 42 waves for the experiments in *a-e* and 15 waves for those in *f-j*.

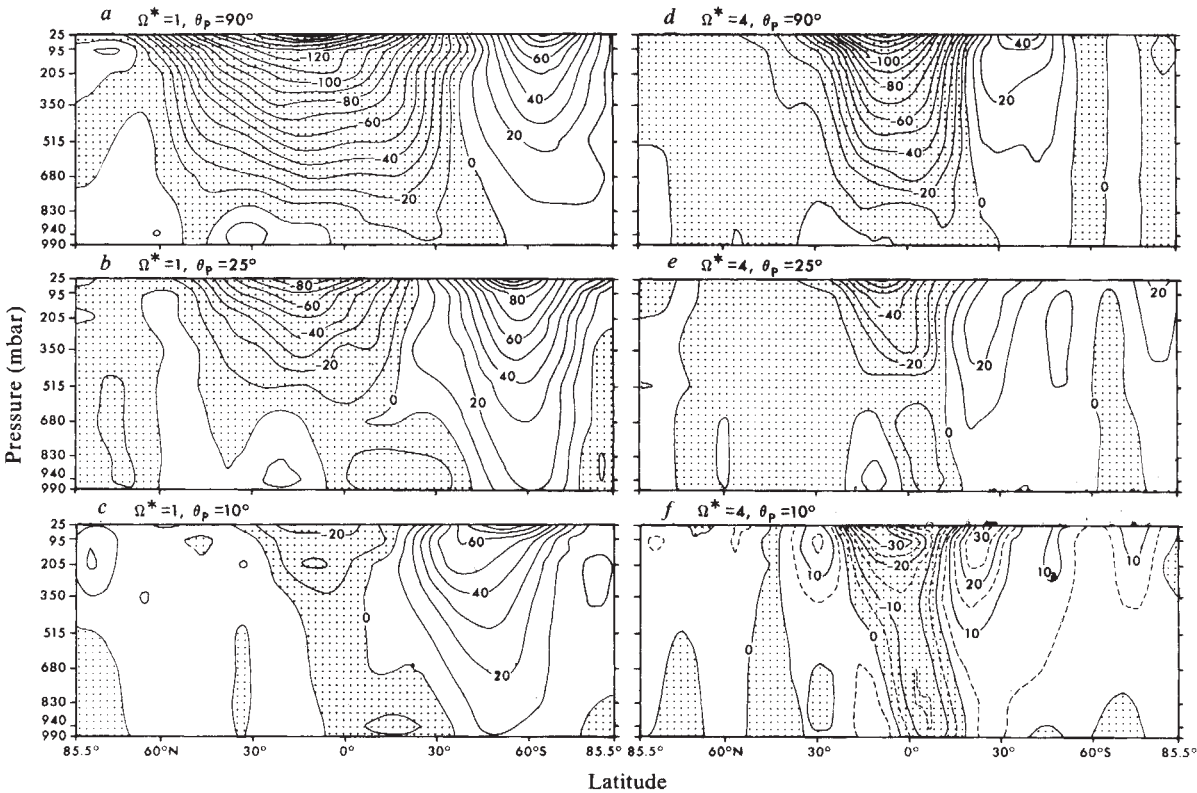


Fig. 2 The mean zonal flow of an Earth-like model atmosphere at different obliquities (θ_p) and relative rotation rates (Ω^*). Similarities may exist between Earth, Mars and *b*, between Uranus and *d*, between Saturn, Neptune and *e*. The solar constant is reduced to 3/4 or 1/2 its normal value when $\theta_p = 25^\circ$ or 90° . The Sun is permanently at the northern hemispheric solstice (left side). Easterlies are shaded; the main contour interval is 10 m s^{-1} and the supplementary one, 5 m s^{-1} . Calculations use a global crescent, 120° in longitude, with a resolution of 15 waves (the solutions are preliminary and of reduced accuracy for the $\Omega^* = 4$ cases).

transform techniques in the horizontal and finite differencing in the vertical. For the radiative heating and cooling calculations, the normal annual-mean distribution of albedo, ozone, carbon dioxide and cloud cover are described as functions of latitude and height, while the variation of water vapour is predicted. The solar declination has its annual-mean values except when we examine obliquity and diurnal effects. For generality, the GCM has a simplified flat, uniformly moist (swamp) surface of zero heat capacity and excludes all ice-related processes. Moist convective adjustment represents small-scale convection and helps maintain vertical (hydrostatic) stability. A quadratic drag law determines the momentum and heat exchanges at the surface. (Full particulars of this GCM may be found in refs 6–9.) Solutions are discussed in terms of the relative rotation rate $\Omega^* = \Omega/\Omega_E$; where $\Omega_E = 7.292 \times 10^{-5} \text{ s}^{-1}$ is the present terrestrial value. θ_p denotes planetary obliquity.

Dependence on rotation rate at equinox

Varying the rotation rate over a wide range of values ($\Omega^* = 0\text{--}8$) produces jets of diverse form and scale in the model atmospheres (Fig. 1). The jets are circumglobal and permanent in form, except at very low rotation rates ($\Omega^* < 1/64$). The double maximum of the idealized terrestrial zonal flow stems from the overlapping of the tropical and extratropical jets at $\Omega^* = 1$ (Fig. 1*d*). These two basic jet forms are more independent and more obvious at higher rotation rates, because the baroclinic eddies are then smaller and more localized. Increased rotation rates also make the tropical jets narrower and the extratropical jets more numerous and more zonally aligned. At $\Omega^* = 8$, the tropical jet is centred on the equator (Fig. 1*a*).

In general, the mean meridional circulations consist of a direct (Hadley) cell equatorward of the tropical jet core, a weaker indirect cell in the poleward part of that jet, and assorted

weaker cells in the extratropical jets. But at lower rotation rates ($\Omega^* \leq 1/4$) the baroclinic eddies cease to exist and a Hadley cell occupies the whole hemisphere (Fig. 1*g–j*). (The ‘tropics’ is defined as being that region influenced by the Hadley circulation. It extends from the equator to 15° N when $\Omega^* = 8$ and to 90° N when $\Omega^* \leq 1/4$.)

The equator-to-pole surface temperature difference generally increases with the rotation rate, from a minimum at $\Omega^* = 0$ to a maximum value (determined by the radiative equilibrium balance) approached at $\Omega^* = 8$, Table 1. A secondary minimum occurs at $\Omega^* = 3/4$ when baroclinic eddies peak in efficiency.

Dependence on obliquity at solstice

During solstice, a planet with a 10° obliquity and terrestrial rotation rate exhibits little latitudinal temperature variation, or motion, in its summer hemisphere (Fig. 2*c*). However, when the obliquity exceeds 20° the summer pole receives the greatest solar heating, resulting in strong pole-to-pole temperature gradients and extensive easterlies (with speeds up to 180 m s^{-1}) and eddies in the summer hemisphere (Fig. 2*a, b*). At $\theta_p = 90^\circ$, a strong temperature inversion in the winter hemisphere excludes eddies from that region. Higher rotation rates reduce the width and amplitude of all currents and also reduce the tendency of temperature maxima to move to higher latitudes as obliquity increases (Fig. 2*d–f*). Consequently, the summer easterlies intrude less across the equator and the flow in the

Table 1 Surface temperatures (K) at the equator and pole of the model atmosphere as a function of relative rotation rate

Ω^*	0	1/8	3/4	1	2	4	8
T_s Equator	292	300	300	305	305	305	310
T_s Pole	280	255	275	270	265	235	230

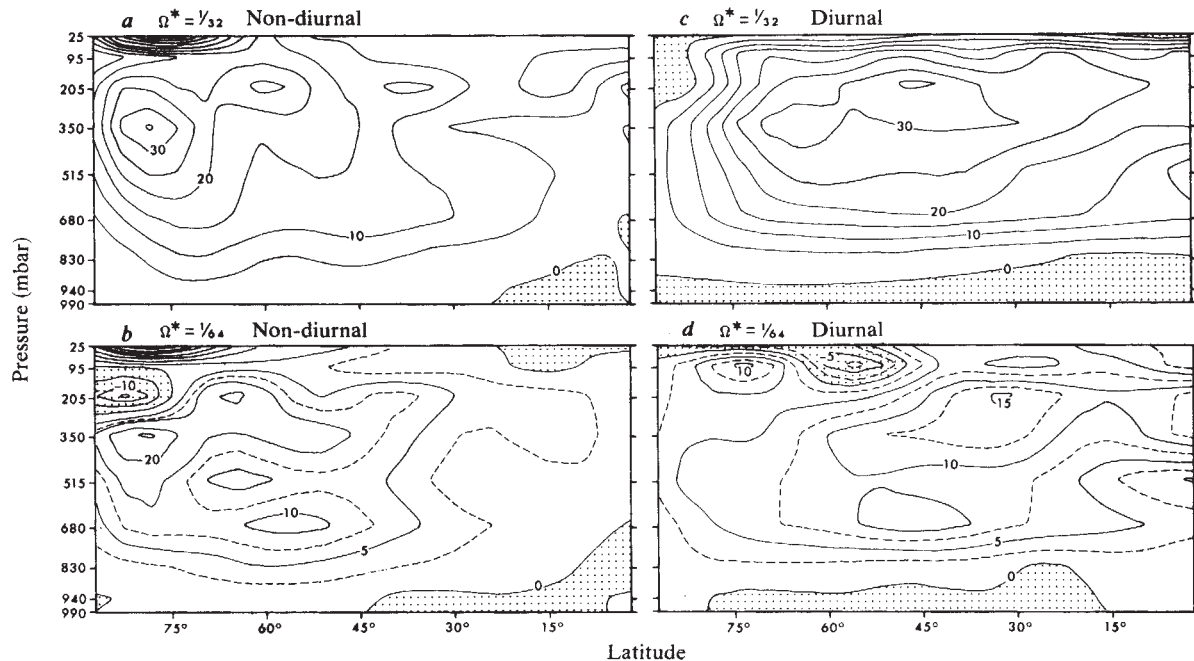


Fig. 3 The mean zonal wind of an Earth-like model atmosphere at two very low rotation rates, with and without diurnal variations in the solar heating. Similarities may exist with Venus. The main contour interval is 5 m s^{-1} and the supplementary one, 2.5 m s^{-1} . Calculations use a full hemisphere and a resolution of 15 waves.

winter hemisphere retains its equinoctial characteristics: a pre-eminent tropical jet and multiple extratropical jets. Interhemispheric heat transport, by the baroclinic eddies and the mean meridional circulation, balances radiative cooling in the unheated winter hemisphere (Table 2).

Dependence on diurnal period

The diurnal variation in the solar heating plays a fundamental role in shaping the circulation of an Earth-like planet only at low rotation rates ($\Omega^* \leq 1/16$).

As the rotation decreases towards these low rates in the nondiurnal system, the axis of the simple tropical (Hadley) jet that now constitutes the entire zonal flow moves poleward until a limit is reached at 80° latitude (Fig. 1*i*). At very low rates ($\Omega^* = 1/32, 1/64$), geostrophy declines and the zonal flow weakens and becomes more complex (Fig. 3*a, b*).

Introducing diurnal variability into the very slowly rotating systems changes their narrow polar jets into broad global currents (Fig. 3*c, d*). The equatorial and subtropical westerly maxima (15 m s^{-1}) produced by the diurnal processes represent powerful currents for a planet whose surface rotates at $< 7 \text{ m s}^{-1}$ (when $\Omega^* = 1/64$).

When $\Omega^* = 1/32$, the diurnal processes are wave-like and moderate; it may then be valid to regard the broad zonal current as being the result of the equatorward redistribution (by the waves) of momentum inherent in the polar jet of the nondiurnal

state¹⁰. When $\Omega^* = 1/64$, the diurnal processes are so strong, and the nondiurnal jet so weak, that there may be no simple association between the diurnal and nondiurnal zonal flows¹¹.

Planetary implications

Earth: The hybrid mix of tropical and extratropical jets that occur at $\Omega^* = 1$ gives Earth the most complex of meteorologies. However, the thermal inertia of the oceans and ice caps reduces the strong seasonal variability normally associated with such an oblique planet. Only in the summer stratosphere are the warm polar temperatures and strong easterlies realized. The influence of obliquity may have been greater during Earth's ice-free-periods, when Ω^* and θ_p were perhaps double their present value⁵, and the circulations were as depicted in Figs 1*c, 2b*.

Mars: Despite great differences in mass and composition, the martian and terrestrial atmospheres have similar forms of circulation. Lacking oceans, however, Mars has greater seasonal variation and, at solstice, the temperature and velocity distributions predicted by a Mars-like GCM³ resemble those given by our simplified Earth model (Fig. 2*c*).

Venus: Venus' zonal circulation consists of a broad retrograde current that varies almost uniformly with latitude and step-like with height. Velocity maxima occur near the equator and in midlatitudes¹²⁻¹⁴. This form of circulation is also exhibited by our Earth-like model when the rotation is very

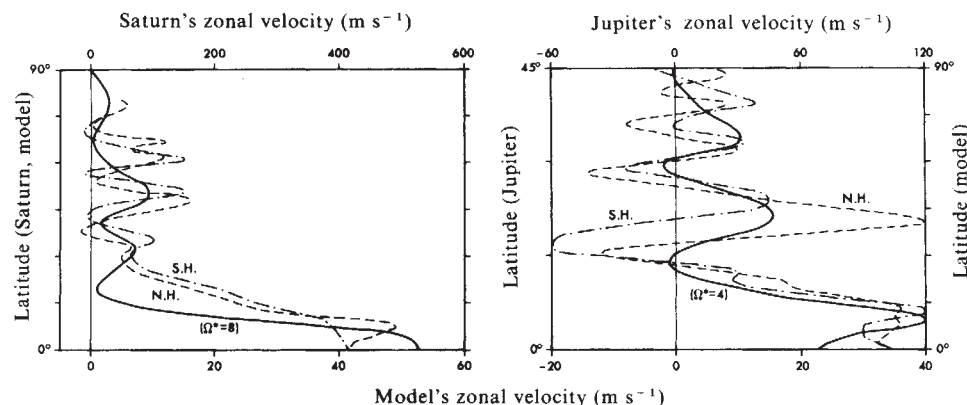
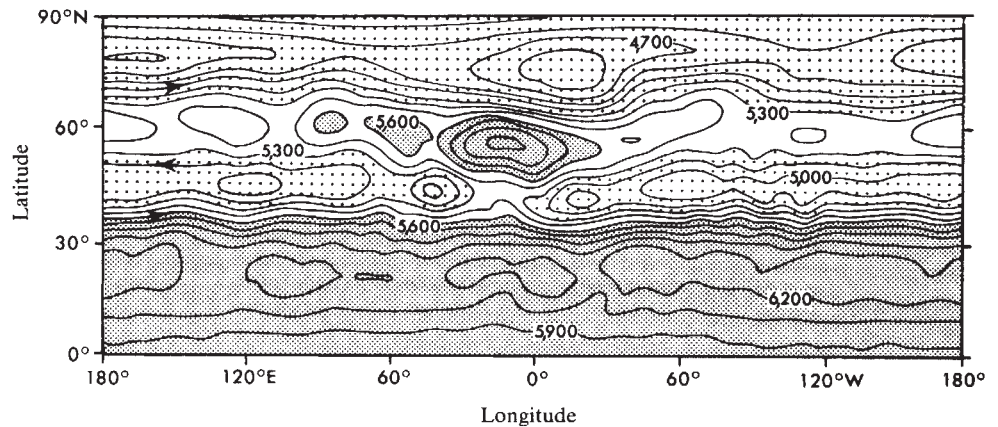


Fig. 4 Latitudinal profiles of the mean zonal velocities of northern and southern hemispheres (NH, SH) and rapidly rotating Earth-like model atmospheres. Adapted from Voyager data^{17,18} and from Fig. 1*a, b* (at 205 mbar): *a*, Saturn and model at $\Omega^* = 8$; *b*, Jupiter and model at $\Omega^* = 4$. Scales are arbitrary.

Fig. 5 The singular vortex resembling the Great Red Spot is produced by a topographic surface anomaly in a rapidly rotating ($\Omega^* = 4$) Earth-like model atmosphere. The 1-km high 'mountain' is centred near the latitude (53°) of zero mean flow (in a geostrophic, anticyclonic-shear zone) and at 0° longitude. Contours of the 500-mbar geopotential surface (a streamfunction) are plotted at intervals of 150 m with shading for values below 5,300 m and above 5,600 m.



slow and the diurnal heat cycle is included (Fig. 3d). Thus Venus seems to behave meteorologically like a slowly spinning, diurnally heated Earth. The diurnal heating component drives the quasi-horizontal turbulent exchanges that determine the form of the zonal wind¹¹ while the nondiurnal heating component drives the meridional exchanges that determine the amplitude of the zonal wind¹⁰.

If we confine the solar heating more to the model's stratosphere, by inserting a high level opaque cloud, a more complex meridional circulation (multiple pole-to-equator cells) occurs but the zonal circulation remains basically unaltered. This suggests that the high level of heat deposition on Venus plays no fundamental role in determining the form of the zonal wind but is vital to the form of the meridional circulation. Stronger winds occur for Venus than for the model mainly because of the greater depth and density of its atmosphere¹⁵.

Table 2 Surface temperatures (K) at summer and winter poles of the model atmosphere as a function of obliquity and relative rotation rate

Ω^*	1	1	1	4	4	4
θ_p	10°	25°	90°	10°	25°	90°
T_s Summer pole	300	310	310	280	320	310
T_s Winter pole	220	180	150	210	180	110

Reduced solar constants (Fig. 2) prevent the temperatures from exceeding 325 K at the summer pole.

Jupiter: Both Jupiter and the Earth-like GCM (when $\Omega^* = 4$) have circulations consisting of a pre-eminent tropical jet and multiple, highly zonal extratropical jets and assorted eddy fields (Fig 4b). If Jupiter does indeed resemble a larger, faster spinning Earth in its meteorology², then we predict that easterly trade winds occur in the lower tropical atmosphere and that Hadley and ageostrophic meridional circulations support the cloud band constituents.

Tropical jets cannot exist if the surface momentum exchange (drag) is excluded, so Jupiter must have a stress-bearing or momentum exchanging sublayer of some sort to be Earth-like in its tropical meteorology. The sublayer needed for tropical jet formation may not be uniform. Solitary topographic bumps (representing magnetic loops, rafts, icebergs, mountains or whatever)¹⁶ inserted into the anticyclonic shear zones of the analogue circulations produce a long-lived anticyclonic vortex, together with a stagnant wake, a current reversal and secondary

vortices (Fig. 5). This flow arrangement resembles that of the Great Red Spot (GRS). Topographic vortices of GRS scale are highly stable because they obey the planetary geostrophic (Burger) equations which, in contrast to the more familiar quasi-geostrophic equations, do not admit dispersive linear-wave solutions (Williams, G. P. and Pacanowski, R., in preparation). Thus, in this Earth-like meteorological view, the existence of the tropical jet and the genesis and permanence of the GRS all point (consistently) towards the presence of some sort of (irregular) sublayer on Jupiter. Such a possibility seems remote but is not inconceivable.

Saturn, Uranus and Neptune: Similar physical configurations should give all the outer planets similar meteorologies and, at least near equinox, zonal circulations like Jupiter's. Observations of Saturn's equatorial circulation reveal some basic differences from Jupiter that may be due to seasonal or other parametric differences (Fig. 4a). A velocity maximum at or near the equator, and a smaller relative amplitude to the extratropical jets, imply that Saturn resembles more an Earth-like atmosphere with $\Omega^* = 8$, than one with $\Omega^* = 4$. The greater strength and extent of Saturn's all-powerful equatorial jet may be due to the wider Hadley cell favoured by a deeper atmosphere.

At solstice, the large obliquity of Saturn and Neptune could lead to easterly winds dominating their summer hemispheres, if the internal heat sources do not reduce the seasonal variations. The extreme obliquity of Uranus and its lack of internal heat sources make the onset of a polar hot spot and powerful easterly winds and eddies inevitable in its summer hemisphere.

Conclusions

The element of unity seen in the above set of solutions suggests that relatively simple principles govern all the known planetary circulations and that these laws can be deduced best by evaluating a comprehensive atmospheric model rather than by trying to reason from individual facts of nature. The extent of planetary unity can be explored relatively simply: by looking for easterly winds deep in Jupiter's tropics or in the summer hemispheres of the other major planets.

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Size and shape in raised mire ecosystems: a geophysical model

H. A. P. Ingram

Department of Biological Sciences, The University, Dundee DD1 4HN, UK

Raised mires are ecosystems in which waterlogged peat accumulates above the level of the surrounding stream system. It has been suggested that waterlogging is maintained by matric forces, but a model involving impeded drainage is in better accord with the structure of the peat and with basic tenets of soil physics. At one site from which enough hydrological and soil physical data are available to conduct a preliminary test, the elliptical shape and proportions of the mire surface profile are in agreement with this model.

RAISED mires or raised bogs¹ which were distinguished from fens by Lesquereux in 1844², were among the earliest types of peatland ecosystem to be recognized, and are known to be one of the world's most widespread types of mire^{3,4}. Their development is marked by the accumulation of peat deposits which, in surface profile, resemble inverted clock glasses⁵. The growth of such a deposit is made possible because it remains perennially waterlogged almost to its upper surface: a feature as paradoxical as it is fundamental, seeing that the central parts of the surface may lie at altitudes up to 10 m above the marginal lagg streams into which the deposit drains. I shall consider here how saturation is maintained in the cupola-like peat deposits of raised mires and, having identified impeded drainage as the mechanism, shall then discuss implications for the shapes of these ecosystems.

Capillary hypothesis

Moore and Bellamy⁶ suggested that domed peat deposits retain their water by matric forces (capillarity), while Gosselink and Turner⁷ believed that 'capillary action' draws water up into raised mires. However, Granlund⁸ had earlier shown experimentally that the zone of saturation would not rise beyond about 0.5 m in *Sphagnum* peat from the higher parts of a raised mire south of Stockholm and this roughly agrees with the maximum rise of 0.3–0.4 m found in a similar situation near Leningrad⁹.

Application of the capillary model of soil pore structure¹⁰

$$h_c = \frac{2\gamma \cos \alpha}{\bar{r}\rho_w g} \quad (1)$$

(where h_c is the height of capillary rise; γ the surface tension of water; α the contact angle, taken to be zero; $\bar{r}$ the mean pore radius, ρ_w the density of water; g the acceleration due to the Earth's gravity) suggests mean pore radii of the order of 30 μm . But to account for a deposit exceeding 5 m in height, the mean pore radius would need to be $<3 \mu\text{m}$, implying complete alteration (maximal humification¹¹) of peat right up to the surface, rather than the more moderate humification generally experienced.

The capillary hypothesis is also unsatisfactory on theoretical grounds. First, it suggests no mechanism for generating a consistent shape, lower at the edges than the centre. Thus it fails to explain the clock-glass profile. Second, it misinterprets the nature of saturation in these deposits. Soil horizons where saturation is maintained by matric forces contain water under tension: they experience negative hydraulic potentials such that, if all water in a raised peat deposit were retained in this way, the water table or surface of zero potential displayed in a dip well would lie at the level of the lagg streams (Fig. 1, A). However, pools frequently occur on raised mire surfaces and, even in their absence, water tables commonly lie within a few tens of centimetres of the surface (Fig. 1, B). Most of the deposit accordingly experiences a positive hydraulic potential. Any

saturated region above the water table is merely a shallow capillary fringe.

Soil structure

Pedologically, an intact raised mire where the peat-forming vegetation has not been destroyed by reclamation or peat extraction may conveniently be described as 'diplotelmic'¹². It comprises two layers of material, namely a core of humified peat known as the 'catotelm' which occupies most of the deposit, overlain by a thin (25–50 cm) 'acrotelm' or 'active layer'^{13–15}. Most of the soil's biological activity and exchange of matter and energy are concentrated in the acrotelm¹⁶. In Holarctic raised mires the top of the acrotelm comprises growing plant material, especially *Sphagnum*, which undergoes alteration by humification below, where it becomes transformed into the partly colloidal material of the catotelm. Because colloidal peat undergoes irreversible alteration on de-watering¹⁷, a condition of the stability and growth of raised mires is that their water tables must stay sufficiently close to the surface to maintain perennial saturation of the entire depth of the catotelm. Thus the thickness of the acrotelm and the maximum depth of the water table (Fig. 1, C and WT) are roughly the same¹⁸, seldom exceeding ~ 0.5 m.

Hydraulics and hydrology

Because matric forces alone are inadequate, it will be clear from Fig. 1 that the body of water saturating the catotelm is inherently unstable. Without atmospheric precipitation it would in time disperse either by evaporation or else sideways into the lagg streams by seepage through the peat. Water bodies of this kind, maintained 'by impeded drainage', or, more accurately, through a dynamic equilibrium between recharge and seepage, are common both in artificially drained land¹⁹ and in more natural situations²⁰. They are conveniently termed 'ground-water mounds'²¹. When developed in a homogeneous, isotropic porous medium through which water flows in accordance with Darcy's law

$$\mathbf{v} = -K \text{ grad } \phi \quad (2)$$

(where $\mathbf{v}$ = bulk flux density; K = hydraulic conductivity; ϕ =

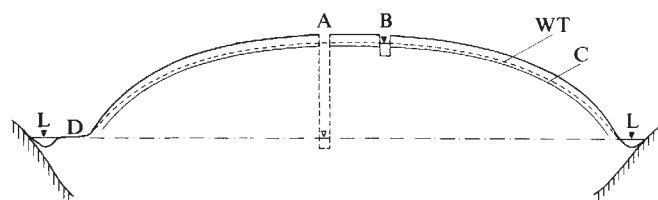


Fig. 1 Schematic sectional profile through a raised mire. A, B, dip wells (see text). C, boundary between top of catotelm and bottom of acrotelm. D, surface of seepage (a phreatic surface at which water emerges) supporting fen vegetation in the lagg. L, lagg streams. WT, water table.

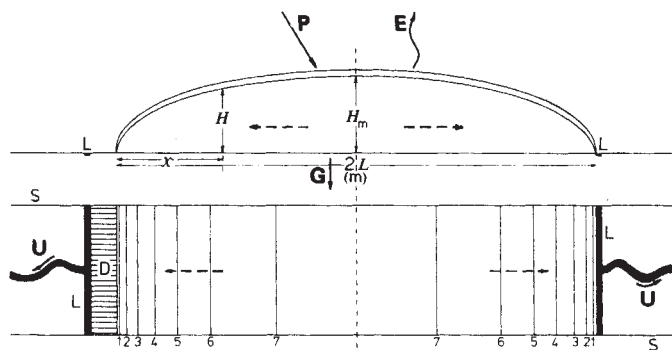


Fig. 2 Groundwater mound in a raised mire, in sectional profile (above) and in plan (below). *D*, *L* as in Fig. 1; *m*, summit and catchment boundary between the two lagg streams; *S*, parallel sides of confining valley with level floor; 1–7, contours of the water table (equipotentials according to the Dupuit–Forchheimer approximation) spaced at equal intervals of altitude. Thick arrows and bold letters: fluxes of water and flux densities (equation (5)). Thin arrows: dimensions of groundwater mound (equations (3) and (4)).

hydraulic potential), the potential distribution must conform with Laplace's equation which can be used, where the geometry is simple, to predict the relationship between height and width of the groundwater mound for any combination of discharge with hydraulic conductivity²². The shape of the mound can also be approximated using Dupuit–Forchheimer theory, which assumes that flow is approximately horizontal, that the equipotentials are vertical surfaces and that grad ϕ is given by the slope of the water table. Thus Childs²³ gave solutions which apply to mounds with equipotentials that are parallel, circular or elliptical in plan. The first case is simplest. Its application to an idealized deposit, shaped like a raised mire and confined in a parallel-sided valley, is shown in Fig. 2. Here the net recharge appears as *U*, the lateral discharge by seepage towards the lagg streams, which are assumed to be at bed level and of negligible depth. The permeability of the deposit is characterized by *K* and the quotient *U/K* is related to the dimensions of the groundwater mound by the expression

$$\frac{U}{K} = \frac{H^2}{2Lx - x^2} \quad (3)$$

which takes the form of the equation of an ellipse. By setting $x = L$, the maximum height H_m of the mound is given by

$$\frac{U}{K} = \frac{H_m^2}{L^2} \quad (4)$$

which corresponds to one limit of the exact solution of Laplace's equation.

Table 1 Water balance, Dun Moss, May 1972–April 1973²⁶

Method	Item	Flux density (mm yr ⁻¹)
Array of standard gauges, diameter 127 mm, exposed at 305 mm above ground level	P	530*
High water tables: lysimeter, checked against U.S.W.B. Class A evaporation pan. Low water tables: short term mass balance when <i>U</i> = 0 (dry periods)	E	317
Short term mass balance when <i>U</i> = 0 (dry periods)	G	26†
By difference	U	187‡
Selection of appropriate period	ΔW	0§

* Compares with $\bar{P} = 951 \text{ mm yr}^{-1}$ for decade May 1970–April 1980.

† Mott's revised estimate.

‡ Equivalent to $5.9 \times 10^{-7} \text{ cm s}^{-1}$.

§ Water levels same at start and finish.

Supposing that the trough of Fig. 2 has a leaky floor, the groundwater discharge *U* becomes one item in a water budget written

$$P - E - U - G - \Delta W = 0 \quad (5)$$

in which all terms are flux densities except ΔW and where *P* = precipitation, *E* = evapotranspiration, *G* = leakage and *W* = storage. ($G \ll U$ for valid application of the Dupuit–Forchheimer approximation).

Groundwater mound hypothesis

These considerations lead to the hypothesis that shape and size in raised mires are controlled by soil physics and hydrology. The hypothesis has the following elements: (1) a diplotelmic soil structure, (2) with perennial saturation of the catotelm, (3) maintained by a groundwater mound, (4) whose dimensions are governed by the water balance, (5) and by the permeability characteristics of the peat, (6) and whose surface, the water table, is confined within a thin acrotelm, (7) so that both acrotelm and ground surface assume an elliptical profile.

It follows from elements (2) and (3) that, with a thin capillary fringe, the catotelm will be coextensive with the groundwater mound when the latter is at its smallest. From elements (4) and (5) it further follows that the critical water balance is that of the driest period through which the mire survives without irreversible desiccation, when the permeability characteristics in question are those of the catotelm alone.

Testing the hypothesis at Dun Moss

To qualify as a test site for the groundwater mound hypothesis a raised mire must meet several criteria. First, human interference with its ecology and hydrology should be minimal. Second, its situation should resemble the model of Fig. 2. Third, its catotelm should have known water transmission characteristics. Finally, relevant hydrometeorological records should be available for several years, including an exceptionally dry period.

Few raised mires are likely to fulfil these stringent requirements completely, but they are met in part by Dun Moss, a small raised mire in east Perthshire (National Grid ref. NO167 558)²⁴. The situation of the mire may be inferred from

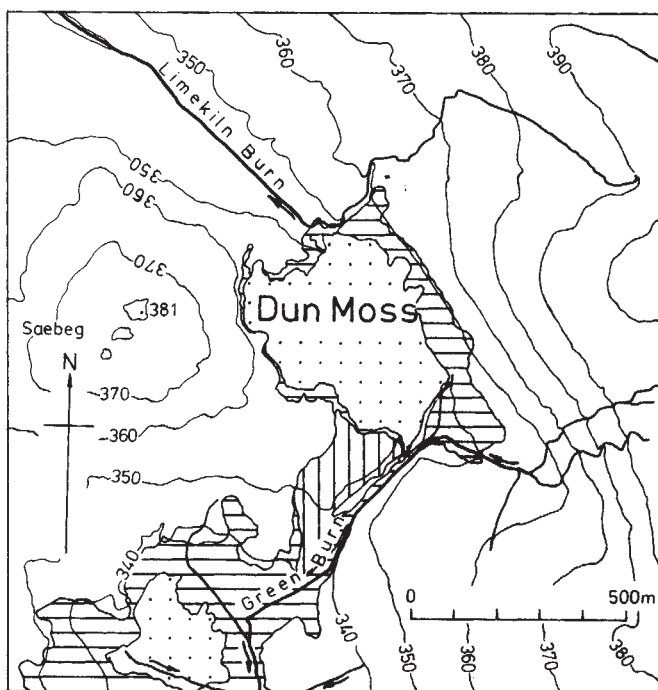


Fig. 3 Physiography and mire types in the vicinity of Dun Moss. ▨, Mire expanse; ▤, marginal lagg fens and so on; ▥, lines, area formerly exploited by peat cutting; arrows, perennial surface streams. Altitudes in m above OD, reproduced from the Ordnance Survey map, Crown copyright reserved.

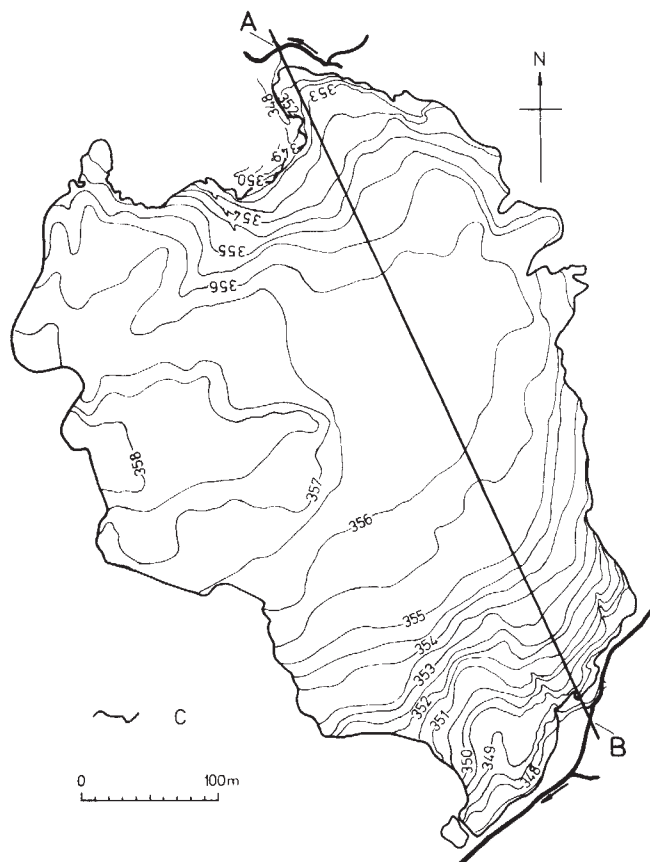


Fig. 4 Physiography of the mire expanse at Dun Moss. AB, line of profile transect connecting the captured headwaters of the Green Burn with the SE-NW reach of the Limekiln Burn. C, boundary of mire expanse. Arrows, lagg streams and so on. Contours in metres, based on a theodolite survey of the hollows on the uneven surface.

Fig. 3. It lies in a north-west trending valley with roughly parallel sides, whose headwaters were deflected south-west across the low ridge south of Saebeg through an overflow channel: a fluvio-glacial feature probably eroded in late Weichselian times. Lagg streams now drain northwards to the Limekiln Burn and southwards to the Green Burn, both with beds at 348.0 m altitude where they touch the mire boundary. The surface of the raised peat deposit is a mosaic of *Sphagnum* hummocks with intervening hollows. Its general shape is shown by the contours in Fig. 4. The profile transect AB is drawn along the axis of the valley, which stratigraphical studies^{25,26} have shown to continue beneath the peat deposit. On this transect the highest point of the mire surface lies at an altitude of 356.2 m, whence $H_m = 8.2$ m. The contour intersections are plotted in Fig. 5. The distance along AB between the lagg streams is 547 m, but of this 27 m is occupied by surfaces of seepage supporting *Carex rostrata* fern communities, mainly adjacent to the Green Burn. Taking 520 m as the correct value of $2L$ for substitution in equation (4) gives a morphometric based estimate of $U/K = 9.95 \times 10^{-4}$ which, when substituted in equation (3), generates the thick curve drawn in Fig. 5. Except near the ends, where the Dupuit-Forchheimer approximation is likely to be weakest, and around the 100-m point on AB where the contours indicate flow diverging from the transect, the points lie close to the hypothetical ellipse.

The site has also yielded data for a preliminary estimate of U/K based on hydrodynamics. There are at present no sophisticated criteria for choosing the time period most appropriate for an estimate of U , but 1 yr is the shortest period during which all the relevant seasonal biological and geophysical processes are represented and which can be selected so that $\Delta W = 0$. Since investigations began at Dun Moss, the driest

year experienced has been May 1972 to April 1973, for which a provisional water balance was drawn up by Mott²⁶ as shown in Table 1. This suggests $5.9 \times 10^{-7} \text{ cm s}^{-1}$ as a tentative minimal estimate of U . Extensive field studies of water transmission through the top of the catotelm at Dun Moss were carried out by Rycroft^{25,27,28}. The results of numerous tests with seepage tubes²⁹ suggested that Darcy's law is only an approximate description of flow in humified peat, but that K values determined in the latter parts of long tests ($t \rightarrow 10^3 \text{ s}$) give a reasonable indication of the permeability characteristics. Stratigraphical analysis showed that the raised peat deposit comprised varying amounts of the remains of *Eriophorum vaginatum* and *Calluna vulgaris* in a matrix of *Sphagnum* species (mostly *S. imbricatum* and sect. *Acutifolia*), generally humified to about H4 on von Post's scale. Consistent sets of results were obtained from H4 *Sphagnum* peat with traces of *Eriophorum* at depths of 70–80 cm at sites C510F and C520F: neighbouring positions within 60 m of the centre of the mire expanse. Variable head tests showed $\bar{K} \rightarrow 2.1 \times 10^{-4} \text{ cm s}^{-1}$ while constant head depletion tests showed $\bar{K} \rightarrow 7.9 \times 10^{-4} \text{ cm s}^{-1}$, suggesting $5.0 \times 10^{-4} \text{ cm s}^{-1}$ as a modal value which we may tentatively accept for the catotelm as a whole, there being no seepage tube technique yet available for use at peat depths exceeding about 1.5 m. Taking these tentative values as best available estimates, we obtain

$$U/K = 1.2 \times 10^{-3}$$

as a hydrodynamically based estimate of the quotient for the driest year experienced. This exceeds the morphologically based estimate by 20% and corresponds with the thin curve in Fig. 5.

Discussion

Ecosystems are entities in which biological, geochemical and geophysical processes interact. Conceptual models of ecosystems may, as with feeding or foraging studies, be fundamentally biological. When concerned with nutrient cycling they are basically geochemical. When dealing with energy capture or water movement their essence may be geophysical. All three elements may be involved in models of phenomena like succession and may contribute to our understanding of whole ecosystems³⁰. Peatlands owe their existence to peculiar soil water regimes. It follows that we should look especially to soil physics and hydrology in our early efforts to build conceptual models of mire ecosystems.

In the present instance, precise conformation between the profile of Dun Moss and its hydrodynamics is scarcely to be expected. Among other complications, it is unlikely that our estimate of U for the driest year for which we happen to have data is actually the lowest discharge experienced. Furthermore the deposit merely resembles the model envisaged in Fig. 2, and its geometry in plan suggests that seepage is neither rectilinear nor parallel to the valley axis throughout the groundwater mound. However, the similarity of the profile to an ellipse whose parameters are in reasonable accord with what is known

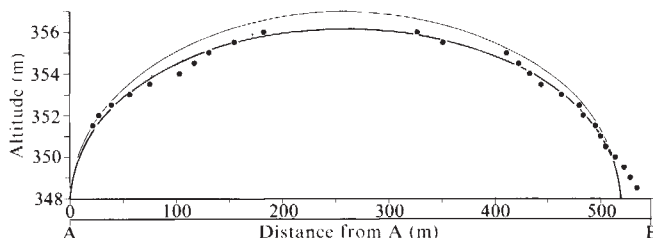


Fig. 5 Profile of mean hollow altitudes on the surface of Dun Moss in the vicinity of transect AB (Fig. 4). Plotted points: contour intersections from Fig. 4. Thick line, Dupuit-Forchheimer ellipse for $U/K = 9.95 \times 10^{-4}$, the morphometric estimate, denoting the shape predicted on the groundwater mound hypothesis. Thin line, the same for $U/K = 1.2 \times 10^{-3}$, the hydrodynamic estimate for the driest year in a decade. (Vertical scale exaggerated 20-fold.)

of the hydrodynamics of the catotelm seems to support the groundwater mound hypothesis.

This hypothesis accords with work by Weber³¹, whose early systematic studies of raised mire ecosystems led him to conclude that they were sustained by meteoric water and impeded drainage. It also postulates a mechanism for the close control of the shapes of these ecosystems. Given that the permeability of moderately altered *Sphagnum* peat (H3-H6) varies rather little with humification³², equation (4) predicts that damper climates will support raised mires of more pronounced convexity (higher ratios of $H_m:L$). Such trends have been reported for Southern Sweden³³ and the Federal German Republic³⁴, while a comparison of the convexity of raised mires in two regions of Finland with similar climates showed little difference³⁵. Equation (3) suggests that growth at all points on the surface of a raised mire is likely to proceed at synchroneal rates, even under fluctuating climates. This agrees with stratigraphical findings

such as those of Aaby³⁶, and with evidence from pollen analysis of cores from various parts of Dun Moss²⁶ which suggests that its shape has remained remarkably constant during some 5 millennia of accumulation.

As a conceptual model, the groundwater mound hypothesis has a secure physical foundation and seems consistent with evidence from various sources. To explore it further we need data on the permeability of the deeper catotelm and on groundwater discharge as a water budget item, not only from Dun Moss but also from other raised mires of relatively simple geometry.

I thank P. J. Mott for permission to quote his water balance computation; R. G. Crawford for help in compiling Fig. 4; D. J. A. Williams for discussions; owners and tenants D. W. Rycroft, R. S. Clymo and Olivia M. Bragg for comments and for access to the site. The data from Dun Moss were obtained during work supported by the NERC.

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Acumentin, a protein in macrophages which caps the 'pointed' end of actin filaments

Frederick S. Southwick & John H. Hartwig

Hematology-Oncology and Infectious Disease Units, Massachusetts General Hospital, Department of Medicine, Harvard Medical School, Boston, Massachusetts 02114, USA

Macrophages have a calcium-insensitive protein which binds to and inhibits monomer addition at the 'pointed' end of actin filaments labelled with heavy meromyosin. This protein, in concert with calcium-sensitive proteins already shown to bind the 'barbed' end of filaments, can lead to complete control of actin filament length in the cytoplasm. The blocking of actin filament ends in low as well as high calcium concentrations would prevent treadmilling in living cells.

HUXLEY¹ first recognized a polarity in actin filaments, and showed that heavy meromyosin bound to actin filaments, giving the appearance of arrowheads attached to the filaments. The direction of the arrowheads defines a 'pointed' and a 'barbed' end of the filaments, and during the contraction of striated muscle, actin moves in the direction of the pointed end. Subsequently, several investigators demonstrated that the association constant for monomer addition is greater at the barbed end of actin filaments decorated with heavy meromyosin than at the pointed end^{2–4}. The barbed and pointed ends of actin filaments labelled with heavy meromyosin have therefore been called the preferred and unpreferred assembly ends, respectively. An observed inequality in dissociation to association rate constant ratio at the opposite ends of filaments at steady state⁴ has given weight to the concept called treadmilling⁵, which

refers to a process in which actin monomers in equilibrium with actin polymers cycle within the filaments from the ends having the lower to the ends having the higher critical concentration. If such treadmilling exists it could cause rearrangement of actin-based structures in the cytoplasm of non-muscle cells⁶. The concept of treadmilling also predicts that anything which prevents an exchange of monomers with the barbed filament end would shorten the filament, and such capping at the pointed end would cause filament elongation.

Another manifestation of actin filament polarity is the binding of different molecules to one end of the filament. Recent work has identified several molecules that bind to the barbed end of actin filaments: these include gelsolin^{7–10}, a protein found in a wide variety of mammalian cells¹¹; villin, a protein very similar to gelsolin and present only in the microvilli of intestinal and

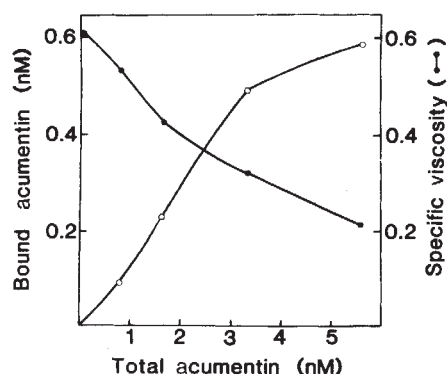


Fig. 1 Binding of acumentin to F-actin and correlation of its binding with changes in the final viscosity of actin. Rabbit skeletal muscle actin³⁰ 0.65 mg ml⁻¹, in 0.8 mM EGTA, 1.25 mM dithiothreitol, 0.05 mM MgCl₂, 0.5 mM ATP and 5 mM imidazole-HCl, pH 7.5, was gel-filtered on Sephadex G-150 and polymerized in the presence of increasing concentrations of acumentin by the addition of 3 M KCl to a final concentration of 0.1 M at 25 °C for 2 h. The specific viscosity of actin was determined in Cannon-Manning capillary viscometers and was 0.61 in the absence of acumentin. The outflow time for water in these viscometers was 48–50 s. The binding of acumentin to G-actin was determined by centrifuging 175 µl of the various actin solutions at 30 p.s.i. in a Beckman airfuge for 1 h to pellet all F-actin present. The amounts of acumentin in the pellet and supernatant fractions were determined by densitometry of Coomassie blue-stained polyacrylamide gels after electrophoresis in the presence of SDS. Acumentin alone did not sediment. Macrophage acumentin migrates as a single polypeptide band of molecular weight 65,000 (Tatsumi *et al.*, manuscript in preparation). This molecular weight was used to calculate the molar concentration of bound acumentin (○).

renal brush border epithelial cells^{12–14}; a protein of *Acanthamoeba*¹⁵; and the cytochalasins^{4,16,17}. Such molecules, in addition to binding to the barbed end of F-actin, stimulate nucleation of actin assembly and shorten the filaments whether added to actin during or after polymerization. The activities of gelsolin and villin are modulated by calcium. Gelsolin and villin bind to actin much more efficiently in the presence of micromolar calcium concentrations than in lower concentrations. The calcium-dependent shortening of actin filaments by gelsolin and villin provides a mechanism by which changes in calcium levels can regulate the length of actin filaments. However, to maintain total control over the filament length, it would be advantageous to cap both ends of the filaments because otherwise some filament annealing and monomer exchange might occur.

Table 1 Effect of macrophage acumentin and gelsolin on the direction of filament growth from F-actin decorated with heavy meromyosin

Type	—◄◄	◄◄—	—◄◄—	◄◄	—	(n)
F-actin alone	2.6 (2)	13 (10)	52 (40)	7.8 (6)	25 (29)	77
F-actin + acumentin	3.0 (2)	38 (26)	4.5 (3)	16 (11)	37 (25)	67
F-actin + gelsolin	20 (15)	1.3 (1)	1.3 (1)	52 (40)	26 (20)	77
F-actin + gelsolin + acumentin	2.0	—	—	84 (88)	24 (25)	102

Actin³⁰, 1 mg ml⁻¹, in 0.2 mM, CaCl₂, 0.5 mM 2-mercaptoethanol, 2 mM Tris-HCl pH 7.5, was polymerized in the absence or presence of gelsolin (molar ratio of 1 gelsolin to 50 actins) by the addition of 0.1 M KCl for 1 h at 25 °C and then incubated with or without acumentin (1 mol acumentin to 25 actins) for an additional 30 min at 25 °C. The filaments formed were then incubated with 1 mg ml⁻¹ skeletal muscle heavy meromyosin for 10 min at 25 °C. 25 µM ml⁻¹ of each was then mixed with 100 µg ml⁻¹ of G-actin and the KCl concentration adjusted to 0.1 M and incubated at 25 °C for 5 min. The protein solutions were then placed in microtitre wells, and a strip of mica previously coated with carbon inserted such that the carbon layer floated on the surface of the solution but was not freed from the mica strip. The mica was then removed, allowing the carbon to re-attach, and inserted in a 1% uranyl acetate solution. The carbon was freed from the mica, Formvar-copper grids were dropped on to the carbon, and the grids were removed from the uranyl acetate solution with a strip of parafilm. The dried grids were photographed in a Philips 301 electron microscope and the negatives enlarged to a final magnification of ×60,000. Data are expressed in per cent with the number of filaments observed in parentheses. —◄◄, Growth of actin from the pointed end only, ◄◄—, barbed end only, —◄◄—, both ends, or ◄◄, lack of assembly onto heavy meromyosin-labelled nuclei, and —, filaments that did not have labelled nuclei attached.

β-Actinin, a protein isolated from skeletal muscle, is the only agent thus far suggested to bind the pointed end of actin filaments^{18,19}. This protein inhibits the annealing of actin filament fragments. When annealing of a mixture of sonic fragments of actin decorated with heavy meromyosin and undecorated fragments occurred in the presence of β-actinin, Maruyama *et al.* had the impression that, compared with controls, more bare filaments attached to the barbed end of decorated segments than to the pointed end¹⁹. However, the barbed end of the decorated filament is in any case preferred for assembly, and therefore it is difficult to show an increase in assembly or annealing from that end. The existence of agents that block the barbed end of filaments makes it possible to ascertain blocking of the pointed end with more certainty. Using this approach we have found that a protein purified from human granulocytes²⁰ and rabbit lung macrophages binds to the pointed end of actin filaments. We propose to name this protein acumentin, from the Latin *acumen* meaning the point.

Acumentin binds and caps the pointed ends of actin filaments

Binding of acumentin to the pointed or unpreferred end of heavy meromyosin-labelled actin filaments was demonstrated indirectly in the electron microscope by observing the assembly of actin nucleated by actin filaments decorated with heavy meromyosin^{2,3} in the presence and absence of acumentin. As shown in Table 1, the addition of decorated actin filaments to a solution of monomeric actin resulted in the growth of filaments from both ends of the nuclei, an observation in agreement with previous findings^{2,3}. In some filaments growth was limited to only one end of the nuclei, with a bias of 5 to 1 favouring the barbed ends of the actin nuclei, the end known to have the most rapid assembly rate⁴. The addition of acumentin to actin nuclei markedly decreased the instances of actin assembly from the pointed ends of the nuclei. Although the findings are consistent with binding and capping of the pointed end of a filament by acumentin, this could also have been due to a second mechanism. The presence of unbound acumentin in the system could potentiate the formation of actin nuclei. Rapid filament assembly from these acumentin would decrease the actin monomer concentration, a condition that would favour the assembly of actin from the barbed or preferred assembly end of actin filaments decorated with heavy meromyosin. As demonstrated in Table 1, acumentin did increase the number of bare filaments.

Experiments using gelsolin ruled out this alternative. The gelsolin-calcium complex prevents assembly at the barbed end⁸ and increases the actin monomer concentration, a condition which favours growth at the pointed end (Table 1). Addition

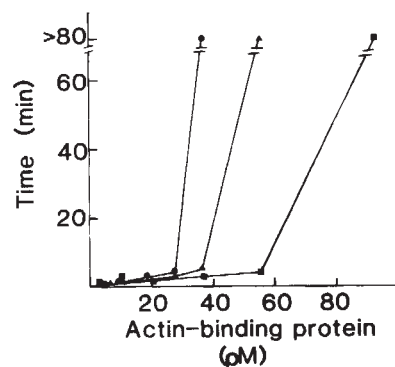
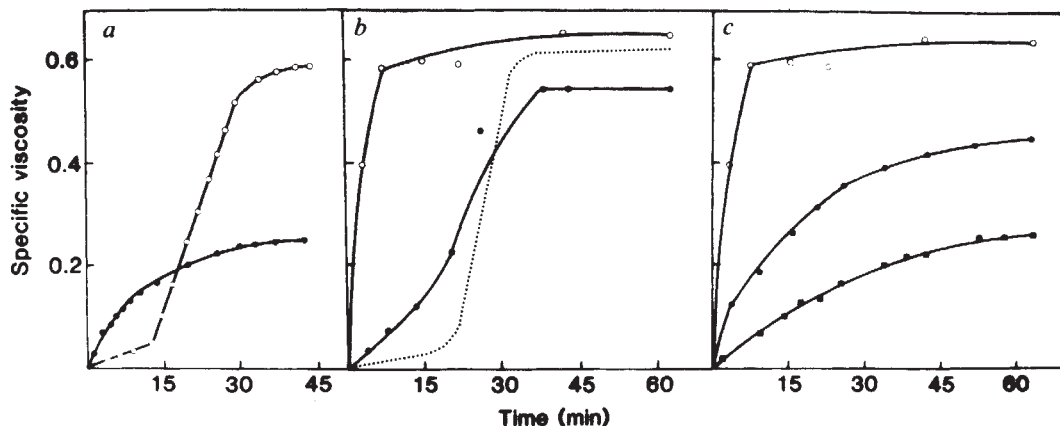


Fig. 2 Effect of increasing concentrations of acumentin on the critical concentration of macrophage actin-binding protein required for incipient gelation of F-actin. Actin, 5 mg ml⁻¹, in buffer A was polymerized by the addition of 3 M KCl to a final concentration of 0.1 M for 1.5 h at 25 °C. The F-actin was then diluted to 1 mg ml⁻¹ in the presence or absence of acumentin and increasing concentrations of macrophage actin-binding protein. The solutions were mechanically mixed before being drawn up into capillary tubes. The final concentrations of acumentin were 0 (●), 20 (▲) and 30 (■) µM ml⁻¹, respectively. Gel points were determined as described by Yin *et al.* using a rolling ball viscometer²³.

Fig. 3 Effects of acumentin on the kinetics of actin polymerization as determined by viscometry. *a*, Effect of acumentin on the nucleation of actin. Actin, gel-filtered on Sephadex G-150, was polymerized at a concentration of 0.65 mg ml^{-1} in 1.5 mM dithiothreitol, 0.175 mM ATP, 0.1 mM EGTA, 0.02 mM MgCl_2 and 5 mM imidazole-HCl, pH 7.5, in the presence (●) or absence (○) of 0.122 mg ml^{-1} of acumentin by the addition of 3 M KCl to a final concentration of 30 mM . *b*, Effect of acumentin on actin filament elongation. Gel-filtered actin, 0.5 mg ml^{-1} , in buffer A was polymerized by the addition of 1 M MgCl_2 to a final concentration of 1 mM in the presence (●) or absence (○) of 0.55 mg ml^{-1} of acumentin for 1 h at 25°C . The filaments formed were used to nucleate actin assembly; $33 \mu\text{l}$ of each was then added to $300 \mu\text{l}$ of 0.5 mg ml^{-1} of G-actin in buffer A. The solution was immediately made up to 20 mM with 3 M KCl and 0.4 mM with 2 M MgCl_2 and its viscosity followed with time at 25°C . The dotted line shows the polymerization of 0.5 mg ml^{-1} of actin in the absence of added acumentin F-actin nuclei. *c*, Additive effects of acumentin and gelsolin on actin filament elongation. 0.5 mg ml^{-1} of actin in the buffer detailed in Fig. 4*b* legend was polymerized in the presence of $33 \mu\text{g ml}^{-1}$ of gelsolin by the addition of 2 M MgCl_2 to a final concentration of 1 mM . The gelsolin-F-actin complexes were then incubated with or without acumentin, 0.55 mg ml^{-1} , for 1 h . $50 \mu\text{g ml}^{-1}$ of F-actin alone (○), gelsolin-F-actin (●) or gelsolin-F-actin-acumentin solution (■) were added to 0.5 mg ml^{-1} of G-actin. The solutions were immediately made 20 mM and 0.4 mM in KCl and MgCl_2 (ref. 2) by addition of 3 M KCl and 2 M MgCl_2 , respectively.



of acumentin to the preparation of labelled nuclei almost completely abolished growth from the labelled filaments, and there was no increase in the number of unlabelled filaments. The data establish that acumentin caps the pointed end. Experiments described below using biophysical techniques are all consistent with the conclusion that acumentin binds to the ends of actin filaments.

Assembly of actin with acumentin shortens the filament length distribution

When actin is polymerized in the presence of acumentin, its final viscosity is decreased relative to that of actin assembled in its absence²⁰. Figure 1 shows the correlation between the capacity of acumentin to bind to actin during polymerization with its ability to reduce the final equilibrium viscosity of actin after assembly. The binding of acumentin to actin filaments increased in proportion to the decrease in final viscosity of the actin solution. This effect of acumentin on the viscosity of actin resulted from the formation of shortened actin filaments, because acumentin does not increase the fraction of monomeric actin in equilibrium with actin filaments. Although the ability of acumentin to reduce the final viscosity of actin was independent of calcium concentration (10^{-8} – 10^{-4} M), its effects on actin viscosity could be inhibited by KCl concentrations above 0.1 M , complete inhibition occurring at 0.3 M KCl (ref. 20). Binding was determined by co-sedimenting acumentin bound to filaments polymerized in its presence. In this assay, the amount of acumentin bound to actin correlated with the degree of filament shortening, and binding increased in almost direct proportion to the concentration of acumentin added. At any given acumentin concentration only $12.6 \pm 2\%$ (mean $\pm$ s.d.) of the added acumentin was bound. As acumentin was present during actin assembly, each molecule theoretically could have bound monomers to form nuclei, suggesting that low affinity rather than a limited capacity was responsible for this low level of binding. The observed linear increase in binding is consistent with the conclusion that acumentin stimulates actin nucleation (Fig. 3*a*), thereby increasing filament number. Therefore, the amount of acumentin bound will be directly related to the number of filament ends.

The conclusion that filaments were shortened is further supported by the finding that acumentin increased, in a concentration-dependent fashion (Fig. 2), the critical amount of cross-linker required to gel a solution of actin. As the critical gel point is inversely related to filament length²¹, acumentin must decrease the average length of actin filaments. The weight-average lengths of actin filaments polymerized in the presence

of 20 and $30 \mu\text{g ml}^{-1}$ of acumentin can be calculated directly from the gel point determinations, using the Flory equation: $V_c = C/X_w$, where V_c is the critical gel point in mol^{-1} , C is the polymer concentration in g l^{-1} and X_w is the weight-average molecular weight of the actin filaments²¹. The calculated length of actin filaments polymerized in the absence of acumentin was $2.44 \mu\text{m}$, and 1.78 and $1.2 \mu\text{m}$ in the presence of 20 and $30 \mu\text{g ml}^{-1}$ of acumentin, respectively.

A comparison of the gel point values with the binding data supports the idea that one acumentin molecule is bound per actin filament. Assuming that 12.6% of the added acumentin was bound to actin filaments, then for 1.0 mg ml^{-1} of actin, 1 mol of acumentin would be bound for every 609 and 409 actin monomers in filaments for 20 and $30 \mu\text{g ml}^{-1}$ of acumentin added, respectively. Dividing these values by the known number of monomers per unit filament length (370 monomers per μm (ref. 22)) gives respective lengths of 1.64 and $1.11 \mu\text{m}$. The values are in reasonable agreement with those determined from the gel point values.

We studied the effect of acumentin on the nucleation and elongation steps of actin polymerization and on filament annealing to analyse the mechanism by which acumentin affects filament length. As shown in Fig. 3*a*, acumentin accelerates the onset of actin polymerization; this suggests that acumentin promotes the nucleation of actin monomers. Growth of filaments from these nuclei may result in the formation of a larger number of shortened filaments relative to actin assembled by spontaneous nucleation, because more nuclei are competing for the monomer pool⁸. However, this effect alone is insufficient to maintain the filaments in a shortened state because such filaments would reanneal with time to a normal length distribution. Short filaments are stabilized at equilibrium by the fact that acumentin binds to their ends (Fig. 3*b*) and prevents annealing and redistributing to a longer length distribution, as amplified below.

To study the elongation phase of filament assembly, nucleation was stimulated maximally by adding nuclei in the form of actin filaments to solutions of monomeric actin. The addition of the F-actin nuclei to monomeric actin resulted in a rapid polymerization of actin, as judged by an immediate increase in the viscosity of the solution (Fig. 3*b*). On the other hand, the addition to monomeric actin of nuclei in the form of actin filaments which had been assembled in the presence of acumentin, promoted a slower initial rate of assembly than did the addition of actin nuclei alone. Therefore, nuclei capped with acumentin, like nuclei reacted with other agents which bind to the end of actin filaments^{8,10,14–16}, are less effective than

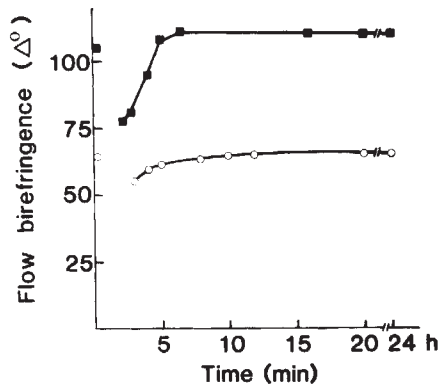


Fig. 4 Effect of acumentin on the annealing of F-actin fragments. F-actin, 0.25 mg ml^{-1} , in 0.1 M KCl , 0.2 mM CaCl_2 , 0.5 mM ATP , $0.5 \text{ mM 2-mercaptoethanol}$, 2 mM Tris-HCl , $\text{pH } 7.5$, was mixed on a mechanical mixer with (■) or without (○) $32 \text{ } \mu\text{g ml}^{-1}$ of acumentin. The flow birefringence and extinction angles of the two solutions were determined as described by Maruyama³¹. The solutions were then sonicated for 40 s on ice and the recovery of birefringence from sonication was then followed with time. F-actin had a final extinction angle of 3° . Acumentin increased the extinction angle to 8° . Velocity gradient was 100 s^{-1} .

actin nuclei in stimulating the growth of actin. This effect is a consequence of the decrease in the number of ends on the nuclei available for binding of actin monomers.

Acumentin and gelsolin have additive inhibitory effects on filament elongation (Fig. 3c). When actin filament fragments capped with gelsolin were added to G-actin solutions, the onset of actin assembly was immediate as judged by the increase in the viscosity of the solution. However, the initial rate of filament assembly was lower than that of polymerization nucleated by addition of actin filaments alone. The addition of acumentin to the nuclei capped by gelsolin further depressed the rate of filament assembly without affecting the onset of polymerization. The combination of the two proteins might at first glance be expected to block both ends of the nuclei, thereby causing actin to assemble as if no nuclei were added. There are two reasons this result was not observed. First, gelsolin affects actin polymerization in several ways. It reduces the number of free nuclei ends by binding to the barbed end of actin filament nuclei. However, gelsolin also 'severs' actin filaments, thereby creating new pointed ends^{23,24}. Moreover, free gelsolin nucleates actin monomers. Second, acumentin also reduces the number of free filament ends by binding to the pointed end of the filaments. However, free acumentin can also nucleate actin monomers. Therefore, as free molecules of acumentin and gelsolin were not removed in the conditions of the experiment shown in Fig. 3c, unbound gelsolin and acumentin would be present in the solution. These molecules could nucleate actin monomers, producing new filaments with one free end. In addition, gelsolin would be expected to produce new ends by cutting filaments. Therefore, the combined effect of gelsolin and acumentin is explained most simply by a reduction in, but not a complete removal of, filament ends.

As shown in Fig. 4, acumentin inhibits the annealing of broken actin filaments. When actin was disrupted by sonication in the absence of acumentin, flow birefringence values recovered rapidly. Shearing of actin filaments in the presence of acumentin on a mechanical mixer or sonication caused an immediate and persistent decrease in the flow birefringence value of the actin, indicative of filament shortening. The decrease in birefringence after shearing is consistent with binding of acumentin to the ends of actin filaments which had been fragmented by shear and with the inhibition of annealing of these capped fragments.

Biological implications

Acumentin binds and caps the pointed end of actin filaments, and potentiates the nucleation step of actin assembly. This effect increases the number of nuclei available for addition of actin

monomers and distributes the resulting polymer mass over more filaments, thus shortening the filament length distribution. The filaments elongate more slowly and remain short because acumentin caps one of their ends. Whether acumentin shortens filaments by actively severing them or by inhibiting broken filaments from annealing is unknown. All experiments involved mechanical shearing of the filaments, and transient filament fragmentation invariably results from these manipulations²⁵.

Phagocytic leukocytes have a layer of distinct cytoplasm located just beneath their plasma membrane, and this cortical cytoplasm is redistributed during cell movement. Electron micrographs of the cortex of these cells reveal the presence of short actin filaments $100\text{--}300 \text{ nm}$ long^{26–29}.

The abundance of acumentin in leukocytes may in part explain the existence of these short filaments. The molar ratio of acumentin to actin in cytoplasmic extracts is 1 to 5 (ref. 20). Assuming that 10% of the acumentin in the cortex were bound to actin, 1 acumentin molecule would cap a filament containing 50 actin molecules or one which was 135 nm long. We presume that acumentin would be constitutively bound to actin filaments, the amount bound being determined solely by its affinity for actin, because its binding to actin is equivalent in high and low calcium concentrations. The gelsolin-calcium complex confers the remaining control and the fine regulation of filament length.

Exchange of actin monomers with the ends of filaments would be totally inhibited if both ends were capped by acumentin and gelsolin, a condition that would occur in the cell when the free calcium level is greater than micromolar. When the free calcium concentration decreases below micromolar concentrations gelsolin dissociates from the barbed end of the filament. Filaments with freed barbed ends would compete with acumentin for the pointed ends of the filaments. Our binding data suggest that the affinity of acumentin for the pointed end of actin filaments is lower than that of actin monomers for the barbed end of filaments⁴, and probably lower than the affinity of filament ends for each other during annealing. High concentrations of actin filaments with free barbed ends could displace acumentin from the pointed ends of other filaments. In these conditions the average filament length would increase.

When the free calcium concentration rises sufficiently, gelsolin would split actin filaments and remain bound to their barbed ends. This would decrease the number of barbed and increase the number of pointed filament ends. In the absence of acumentin, residual free barbed filament ends would anneal with the pointed ends of other filaments and free monomers could also bind to the pointed ends. Capping of the pointed ends by acumentin would prevent either this filament annealing or monomer addition, thereby conferring a greater degree of precision to the control of actin filament length by the calcium-gelsolin complex.

Furthermore, the interaction of acumentin and gelsolin with actin could permit rapid changes in lengths of existing filaments without concomitant alterations in a pool of monomeric actin which might cause the uncontrolled formation of new filaments. Finally, the presence of an agent that constitutively blocks a filament end, renders unlikely the existence of actin treadmilling in the living cell.

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Protamine is an inhibitor of angiogenesis

Stephanie Taylor & Judah Folkman*

Department of Surgery, Children's Hospital Medical Center and the Departments of Anatomy and Surgery, Harvard Medical School, Boston, Massachusetts 02115, USA

Protamine is shown to be a specific inhibitor of angiogenesis. The compound inhibits the capillary proliferation observed in embryogenesis, inflammation, certain immune reactions and the growth of solid tumours.

ANGIOGENESIS, the growth of new capillary blood vessels, is important in normal processes such as development of the embryo, formation of the corpus luteum and wound healing. It is also a component in pathological processes such as chronic inflammation, certain immune responses and neoplasia^{1–3}. Furthermore, angiogenesis is a property of most solid tumours and is necessary for their continued growth⁴. Consequently, we have hypothesized that an angiogenesis inhibitor might be used to control tumour growth⁵.

During our early studies of angiogenesis we observed that mast cells accumulated at a tumour site *before* the ingrowth of new capillary sprouts, but that mast cells alone could not initiate angiogenesis⁶. We later postulated that mast cells might facilitate the continuous migration⁷ of capillary endothelial cells towards the solid tumour. When capillary endothelial cells were cloned and carried in long-term culture⁸, and a quantitative assay was devised to measure their migration rate⁹, we found that heparin released by mast cells increased the migration (chemokinesis) of capillary endothelial cells *in vitro*¹⁰. Protamine, an arginine-rich basic protein of 4,300 molecular weight (M_r), found only in sperm and known for its capacity to bind heparin, blocked the ability of mast cells and heparin to stimulate migration of capillary endothelial cells¹⁰.

We now show that protamine is a specific inhibitor of stimulus. Protamine released locally prevents the neovascularization induced by an inflammatory agent or by an immune reaction and it inhibits capillary proliferation in the embryo. Protamine also inhibits tumour angiogenesis and subsequent tumour growth when it is applied locally, but in only a few cases when it is administered systemically. It has no effect on established capillaries that are not proliferating. We further show that heparin can enhance the intensity of angiogenesis induced by tumour extract *in vivo* but that heparin alone cannot initiate angiogenesis.

Inhibition of angiogenesis in the embryo

The effect of protamine on growing embryonic vessels was investigated using chick embryos of different ages. Capillaries appear in the yolk sac at 48 h and grow rapidly over the next 6–8 days. Protamine in methylcellulose disks applied locally inhibited capillary growth and produced a large avascular zone in the yolk sac (Fig. 1), whereas control embryos implanted with empty disks did not develop avascular zones.

Heparin added to the protamine disk prevented the develop-

ment of the avascular zone (Fig. 1). The non-anticoagulant fraction of heparin¹¹ was equally effective in this action, while heparin alone did not cause an avascular zone.

In contrast, protamine had no effect on mature, non-growing¹² vessels studied on the chorioallantoic membrane at day 10. However, protamine applied to younger proliferating vessels of the day 5 or 6 chorioallantoic membrane produced a large avascular zone within 48 h.

Inhibition of tumour angiogenesis

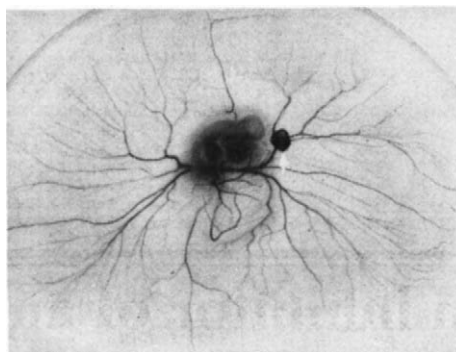
The first indication that protamine could inhibit tumour angiogenesis came from studies of heparin on the chick chorioallantoic membrane (CAM). When 100 µg of tumour extract (partially purified for angiogenesis activity from human hepatoma cells)⁹ was placed on the CAM, new capillary growth was elicited within 48 h in 90% of the eggs. Addition of heparin (6 µg, that is, 1 unit) reduced to 25 µg the amount of tumour extract required to elicit neovascularization in 100% of eggs, and reduced the interval between implantation and capillary growth to 24 h (Fig. 2). Heparin alone had no effect. Addition of protamine just sufficient to neutralize heparin (12 µg) eliminated the angiogenesis enhancing effect of heparin. However, when protamine was increased to 20 µg, it prevented all angiogenesis induced by tumour extract (25 µg) (Fig. 2).

A further test used a sustained release pellet¹³ of protamine positioned between tumour and normal vessels in the rabbit cornea¹⁴, allowing quantification of the inhibition of new capillary proliferation as a function of the rate of linear capillary growth. A protamine pellet juxtaposed to a V2 carcinoma implant almost completely inhibited capillary growth. In contrast, in the untreated eyes, tumours were vascularized by hundreds of new capillary sprouts and grew rapidly. Tumours in the protamine treated eyes did not become vascularized until the protamine pellet was removed. The mean vessel growth rate in the protamine-treated eyes was 0.02 ± 0.01 mm per day compared with 0.25 ± 0.07 mm per day in the untreated eyes (Figs. 3a, b and 4).

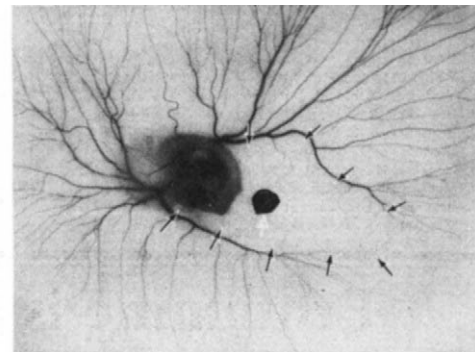
A more rigorous test of an angiogenesis inhibitor is to implant tumour directly into vascular tissue. Thus when V2 carcinoma and protamine pellets were implanted in a subcutaneous pouch¹⁵ in the rabbit ear, the density of neovascularization (observed by transilluminating the ear) was markedly reduced in comparison with tumour in the opposite ear not exposed to protamine. Although vessel growth rates could not be quantified, tumour growth could be. Protamine-treated tumours grew at a mean rate of 8 ± 1 mm³ per day compared with 68 ± 5 mm³ per day for untreated tumours (Fig. 5). By histological section, the protamine-treated tumours, while still

* To whom correspondence should be addressed: Children's Hospital Medical Center, 300 Longwood Avenue, Boston, Massachusetts 02115, USA.

Fig. 1 Inhibition of angiogenesis by protamine in the chick embryo yolk-sac vascular membrane. Fertilized embryos are placed in a Petri dish on day 4 and cultured in a humidified incubator in 5% CO₂ as previously described³². Protamine sulphate (Calbiochem) is dissolved in distilled H₂O to make 14.3 µg µl⁻¹. 500 µl of this solution is added to 500 µl of 1% (w/v) methylcellulose (in distilled water, previously sterilized by autoclaving). Aliquots (7 µl) of this mixture are pipetted onto Teflon moulds of 3.2 mm diameter and allowed to dry (J. Barlow and J.F., unpublished). The resulting methylcellulose disk contains 50 µg protamine and can be peeled away from the Teflon mould. For control disks, 500 µl H₂O is substituted for the protamine. For photographic purposes, India ink can be added to the methylcellulose (2 µl per 100 µl). A methylcellulose disk (white arrow) was placed at the advancing edge of the vascular membrane on day 4 and the resultant avascular zone (black arrows) measured on day 6. The outlines of the yolk sac and of the avascular zone were traced on top of the Petri dish cover and converted to area with a Zeiss MOP-3 digital image analyser (Carl Zeiss). Forty-three embryos were implanted with protamine disks. The mean area of the vascular membrane on day 6 was 24.8 ± 1.0 cm². The mean area of the avascular zones produced by protamine was 3.0 ± 0.4 cm², or 12.5% of the original vascular area. In 43 control embryos implanted with empty disks, the mean area of the vascular membrane was 23.6 ± 1.0 cm². There was no avascular zone in these embryos. Heparin (25 µg) added to the protamine disk prevented the development of the avascular zone. The non-anticoagulant fraction of heparin¹¹ was equally effective in preventing the protamine-avascular zone. Heparin alone did not cause an avascular zone. While the size of the avascular zone was dose related to protamine, it was not specific for protamine. Extremes of pH and osmolarity could also produce an avascular zone.



Control



Protamine

viable, were either avascular or were penetrated only sparsely by capillaries. In contrast, the untreated tumours were pervaded by a dense capillary network.

Inhibition of inflammatory angiogenesis

To determine whether protamine could inhibit inflammatory angiogenesis¹⁶, a focus of chronic inflammation was established in the rabbit cornea by implanting silica particles. In each of six rabbits, a protamine pellet (prepared as described in Fig. 3 legend) was implanted between the silica and the normal vascular bed. An empty pellet was implanted in the opposite eye. New capillaries appeared at 2 days in the untreated eyes and grew towards the silica at a mean rate of 0.2 ± 0.02 mm per day. By contrast, in the protamine-treated eyes the mean vessel growth rate was 0.06 ± 0.01 mm per day. When the protamine pellet was exhausted or removed, new capillaries advanced towards the silica at the same rate as in untreated eyes.

Inhibition of immune angiogenesis

To determine whether protamine could block immune angiogenesis¹⁷, fragments of rabbit lymph node were implanted in corneal pockets of nine outbred rabbits. Either a protamine pellet or an empty pellet was implanted between the node and the normal vascular bed. In the absence of protamine, new capillaries entered the cornea by day 4 and advanced towards the lymph node at a mean rate of 0.20 ± 0.03 mm per day. In the presence of protamine, angiogenesis was suppressed completely until day 8, when a few vessels began to grow at 0.05 ± 0.03 mm per day.

Systemic administration of protamine

Although the systemic administration of protamine was limited by its toxicity at high doses (lethargy, weakness and occasionally sudden death), it has, within the tolerated doses, been used to test the inhibition of growth of four types of lung metastases and three of their subcutaneous primary tumours.

Protamine concentrations in the lung were fivefold greater than in the subcutaneous tissue, and 40-fold greater than in the skin.

Lung metastases. To test whether systemically administered protamine was an effective inhibitor of tumour growth, mice with lung metastases were treated with subcutaneous protamine at 12-h intervals (Fig. 6). When mice which had received Lewis lung tumour cells, B16 melanoma cells (subcutaneous strain) or B16 melanoma cells (tissue culture strain) either intravenously (i.v.) or subcutaneously (s.c.) were treated with a well tolerated dose of protamine (60 mg per kg, s.c., every 12 h), there was 77–92% inhibition of mean lung metastases

tumour volume compared with saline-treated animals. The number of lung metastases did not differ significantly between protamine- and saline-treated animals with the exception of the two strains of melanoma.

Similarly, when rats which had received Walker 256 carcinoma cells i.v. were treated with a well tolerated dose of protamine (120 mg per kg, s.c., every 12 h), there was 97% inhibition of mean lung metastases tumour volume compared with saline-treated animals (Fig. 6). The number of metastases was also reduced: there were 3 metastases per rat in the protamine-treated animals compared with 64 metastases per rat in the saline-treated animals (Fig. 6).

Subcutaneous tumours. The growth of neither Lewis lung carcinomas nor B16 melanoma (subcutaneous strain) when implanted s.c. was significantly inhibited by protamine except for some inhibition of the former at highly toxic doses (135 mg per kg). However, systemic protamine did inhibit the growth of subcutaneous tumours of B16 melanoma (tissue culture strain), as will now be described.

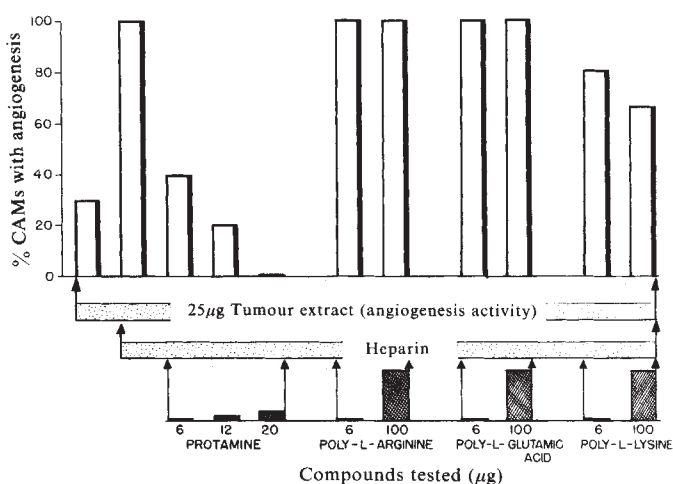


Fig. 2 Angiogenesis on the chick chorioallantoic membrane (CAM). Tumour extract (25 µg, from hepatoma cells⁹) in 5 µl H₂O was placed on the centre of a round plastic coverslip (Thermanox, 15 mm diameter) (J. Barlow and J.F., unpublished data). To each disk was added another 5 µl aliquot containing either heparin (6 µg) or one of the test compounds. The coverslip was allowed to dry, placed on the CAM of 9-day-old embryos and viewed 24 h later with a ×12 stereomicroscope. Angiogenesis was present if new capillaries converged on the spot in the centre of the coverslip. Controls were poly-L-arginine (*M_r* 130,000, Sigma), poly-L-glutamic acid (*M_r* 10,000) and poly-L-lysine (*M_r* 3,000). The five bars on the left represent 50 eggs each. The remaining six bars to the right represent 15 eggs each.

Fifty-two C57BL/6 mice received 4.6×10^7 melanoma tissue culture strain F2¹⁸ s.c. (smaller inocula of 10^3 , 10^4 and 10^5 cells also produced tumours, although much later). Half of the mice received protamine 60 mg per kg, s.c., every 12 h in a remote site and the other half received saline. All tumours took and grew at approximately the same rate in both protamine- and saline-treated animals until day 5 when the tumours were nearly 0.05 cm^3 and had become vascularized. The protamine-treated tumours then slowed their growth (0.05 cm^3 per day) until day 18 when they either stopped growing or began to regress. The saline-treated tumours continued to grow rapidly over the same period (0.23 cm^3 per day). In 13 (50%) of the protamine-treated mice, tumour regressed completely. It was necessary to lower the protamine dose by approximately one-half once regression was complete. These mice remained tumour free after protamine was discontinued. Eight (30%) died while the tumour was undergoing rapid necrosis. Two mice died with melanoma ascites after the primary tumour had disappeared. In three mice, tumours underwent incomplete regression and remained as small, barely visible lesions. Their tumour growth resumed whenever protamine was discontinued, and they were dead by

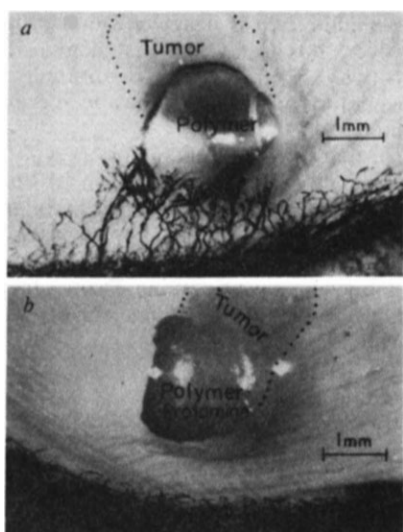


Fig. 3 Inhibition of tumour angiogenesis in the rabbit cornea by protamine. Polymer pellets of ethylene vinyl acetate (EVA) copolymer, of $\sim 1 \text{ mm}$ diameter were impregnated with $1,000 \mu\text{g}$ protamine sulphate as previously described¹³. The pellets were coated with 2% EVA in methylene chloride, dried for 3 h and sterilized by UV light for 2 min. The pellets were implanted in a pocket in the rabbit cornea, 1 mm from the limbus. A 1 mm^3 piece of V2 carcinoma was implanted distal to the polymer, 2 mm from the limbus¹⁴. In the opposite eye of each rabbit, control polymer pellets that were empty were similarly implanted in juxtaposition to the tumour. By spectrophotometric analysis *in vitro*, the pellets released $400 \mu\text{g}$ protamine on day 1. This sustained release declined exponentially until day 4, when the pellets released an average of $15 \mu\text{g}$ per day thereafter, for the next 15 days. As capillary blood vessels grew towards the tumour implant, maximum vessel length was measured every 3 days with a stereoscopic slit-lamp at $\times 10$ ($\pm 0.1 \text{ mm}$). At day 10 a typical rabbit was killed and India ink was injected into each carotid artery. The corneas were removed and photographed with a stereoscope. *a*, New capillary blood vessels growing towards the tumour and passing over the blank polymer. *b*, In the presence of the protamine pellet (opposite eye), new capillary vessels at the edge of the cornea do not enter the cornea. Histological sections showed viable tumour in each cornea.

day 68. The saline-treated animals died with massive tumours ($17.8 \pm 0.4 \text{ cm}^3$) by day 30. Using the same strain of melanoma, this experiment was repeated eight times over a 2 yr period with essentially similar results (tumour regression in $\sim 50\%$ of the animals). After a large tumour had regressed to become no longer visible, it was necessary to continue the lower dose of protamine for at least 2 more weeks, otherwise the tumour recurred. When mice that had been tumour free and not receiving protamine for 1–11 months received a second s.c. inoculation of the same strain of melanoma cells, new tumours developed and were also susceptible to protamine inhibition.

Thus, the first tumour regression apparently was not accompanied by a strong immune reaction.

Controls

To control for the specificity of protamine as an angiogenesis inhibitor, compounds similar in structure or charge density to protamine were tested against tumour angiogenesis in the CAM and against growing embryonic vessels on the yolk sac. Poly-L-arginine, poly-L-glutamic acid and poly-L-lysine produced no inhibition of angiogenesis at concentrations two to four times the protamine concentration that was inhibitory (Fig. 2). At five times the protamine concentration, poly-L-lysine weakly inhibited tumour angiogenesis in the CAM but did not inhibit the growth of yolk sac vessels. These compounds were all lethal when applied at concentrations greater than five times the protamine concentration. Platelet factor 4 and major basic protein from eosinophils have a high affinity for heparin. They both produced avascular zones at approximately one-half the concentration of protamine.

As another control of protamine specificity, mixtures of heparin and protamine (1:2) were assayed in the chick embryo (Fig. 1). Both the commercial anticoagulant heparin (Sigma) and the non-anticoagulant fraction¹¹ (courtesy of Dr Robert Rosenberg) neutralized the anti-angiogenesis activity of protamine in the yolk sac and on the CAM. Heparin (Sigma) was also injected into tumour-bearing mice simultaneously with protamine (but at a different site). Inhibition of tumour growth was abolished; tumour size and mouse mortality were the same as for mice injected with saline alone (data not shown).

To exclude the possibility that protamine inhibition of tumours might be caused by direct cytotoxicity, tumour cells were exposed to protamine *in vitro*. Protamine was neither cytostatic nor cytotoxic to V2 carcinoma, B16 melanoma (tissue culture strain), Lewis lung or Walker cells at concentrations of $50\text{--}500 \mu\text{g ml}^{-1}$. Growth suppression began at $500 \mu\text{g ml}^{-1}$ for Walker cells, but melanoma, V2 and Lewis lung cells were not suppressed at $1,000 \mu\text{g ml}^{-1}$. In fact, growth of V2 carcinoma was stimulated to 55% above control by a protamine concentration of $100 \mu\text{g ml}^{-1}$, and Lewis lung cells were stimulated to 37% above control by a protamine concentration of

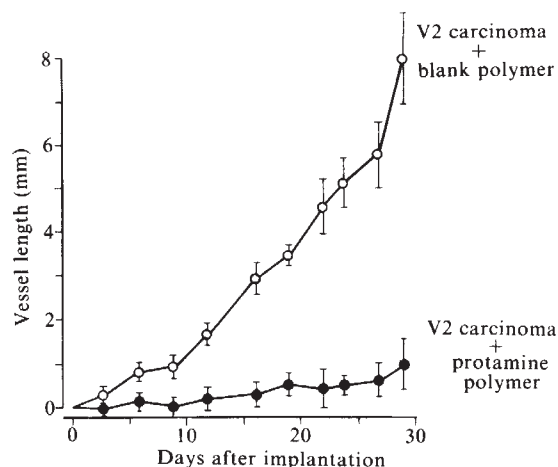


Fig. 4 Measurement of capillary growth rate in the rabbit cornea. Series of nine rabbits with V2 carcinoma in each cornea accompanied by a protamine pellet (●) or empty pellet (○) were used as described in Fig. 3 legend. In the presence of protamine, capillary growth is suppressed until the week 3 (when protamine release from the polymer pellet declines). In the eyes containing a blank pellet, tumours all became vascularized and grew to a large exophytic mass, necessitating the death of these animals by about 30 days. In a parallel experiment (data not shown), in which both eyes of an animal were treated with protamine, capillary growth resumed within 3 days of removal of the pellet. There was subsequent rapid tumour growth. Protamine pellets implanted in the absence of tumour did not induce neovascularization. Measurements are expressed as mean $\pm$ s.e.m. here and in all subsequent figure legends. Eyedrops of protamine in Ringer's solution (100 mg ml^{-1}) applied three times per day, did not inhibit capillary growth. The eyedrops caused no detectable irritation in the normal eyes of rabbits. Systemically administered protamine failed to inhibit capillary growth in the cornea.

500 $\mu\text{g ml}^{-1}$. These concentrations exceed any local concentrations of protamine achieved *in vivo* by sustained-release pellets. Furthermore, when protamine was administered systemically, its peak uptake in subcutaneous melanoma was 70 μg per 100 mg of tumour at 1 h. This is equivalent to 0.001 μg per 1,000 cells (assuming that a 100 mg tumour contains at least 10^7 cells). The melanoma cells *in vitro* grew maximally at 2 μg per 1,000 cells, that is, at more than 2,000 times the protamine concentration achieved *in vivo*.

To determine if protamine was cytotoxic to rapidly dividing cells *in vivo*, melanoma-bearing mice treated with protamine or saline for 11 days received 80 μCi ^3H -thymidine and were killed 5 h later. The percentage of ^3H -thymidine labelled cells in the bone marrow was similar for the protamine-treated (20%) and saline-treated mice (17%). In the saline-treated tumours, 17% of the tumour cells were labelled. There was no necrosis. In contrast, the regressing protamine-treated tumours were marked by a large necrotic centre and a few outer layers of viable cells. The labelling index of the rim of viable cells was 16%, not significantly different from the saline-treated tumour.

To exclude the possibility of cumulative toxicity at the 60 mg per kg dose, 10 non-tumour-bearing mice received protamine (60 mg per kg, s. c., every 12 h) for 1 yr, beginning at age 6 weeks. Their weight gain and activity were the same as for 10 saline-treated mice throughout this period, and all 20 mice were alive at the end of 1 yr.

Discussion

These studies show that protamine is an inhibitor of angiogenesis in the four species tested, irrespective of whether the angiogenic stimulus is embryological, neoplastic, inflammatory or immunogenic.

The mechanism by which protamine inhibits angiogenesis is unclear. However, previous *in vitro* studies suggest that heparin modulates the rate of migration of capillary endothelium¹⁰. The specific binding of protamine to heparin could block the linear migration of capillary endothelial cells, thus interfering with a crucial step in capillary formation⁷. The anticoagulant function of heparin apparently is not involved in this reaction, because the non-anticoagulant fraction of heparin is capable of reversing the anti-angiogenesis activity of protamine. Although coagulation studies remained normal in animals treated with protamine, it is possible that protamine may modify fibrin deposition in the neovascular bed induced by tumours^{19,20}. Furthermore, the disparity between the effect of protamine on lung metastases and subcutaneous tumours seems to be due to differences in the tissue uptake of protamine (unpublished data).

These experiments do not prove unequivocally that the angiogenesis-inhibitory activity of protamine is responsible for its anti-tumour effect. However, indirect evidence in support of this conclusion is based on four observations: (1) when protamine is removed from the cornea, capillary growth resumes *before* tumour regrowth begins; (2) histological sections from protamine-treated animals show many microscopic lung metastases that remain avascular, in contrast to saline-treated animals where vascularized tumours predominate; (3) tumour regression in mice does not seem to be immunologically mediated, because lymphocytic infiltration is minimal or absent, and when animals taken off protamine after complete tumour regression are re-inoculated with melanoma cells, tumours grow as before; (4) protamine is neither cytostatic nor cytotoxic to tumour cells *per se* at the doses used.

Four lines of evidence argue that protamine does not act directly on tumour cells: (1) tumour cells in culture grow well at protamine concentrations greater than the peak concentrations of protamine in tumour; (2) the early growth of the protamine-susceptible strain of melanoma (before neovascularization) in protamine-treated mice is not significantly different from that of melanomas in saline-treated mice; (3) the ^3H -thymidine-labelling index of bone marrow and viable tumour cells does not differ significantly between protamine- and saline-treated mice; (4) melanoma cells in ascites proliferate

during protamine treatment even while the solid primary tumour regresses.

The effectiveness of protamine in inhibiting the growth of lung metastases and its relative ineffectiveness against many subcutaneous tumours might be partly explained on the basis of differential protamine uptake by the two tissues. However, there is no explanation for the finding that strains of tumour implanted s.c. should have different susceptibility to protamine. Some tumours have been found to contain two subpopulations of neoplastic cells—those that can stimulate angiogenesis and those that cannot²¹—and it is possible that the ratio of these two subpopulations dictates the intensity of angiogenesis for a given tumour mass. A second possibility is that different tumour strains might secrete different amounts of glycosaminoglycans that would bind protamine in competition with heparin. A third speculation is that in protamine-resistant tumours there may be more mature vessels. Little is known about the extent to which new capillaries within a tumour convert to mature capillaries and venules (that is, with intact basement membrane, and accumulated pericytes or smooth muscle). Finally, there may be important differences in mast cell content of tumours that would account for different responses to protamine.

Angiogenesis inhibition is a newly found property of protamine. However, this is not the first demonstration of the antitumour activity of protamine, as antitumour activity of protamine or mixtures containing it has been previously found in mice and humans^{19,22–26}.

It is possible that angiogenesis inhibitors will eventually be used clinically in those diseases common to ophthalmology, dermatology and rheumatology where neovascularization is the dominant pathology, and in certain neoplasms that are the most highly angiogenic, such as brain tumours. It is, however, much too early to know whether protamine or any other inhibitor of angiogenesis, conceivably including some of endogenous origins^{27–31}, will be of any clinical value. Protamine is toxic

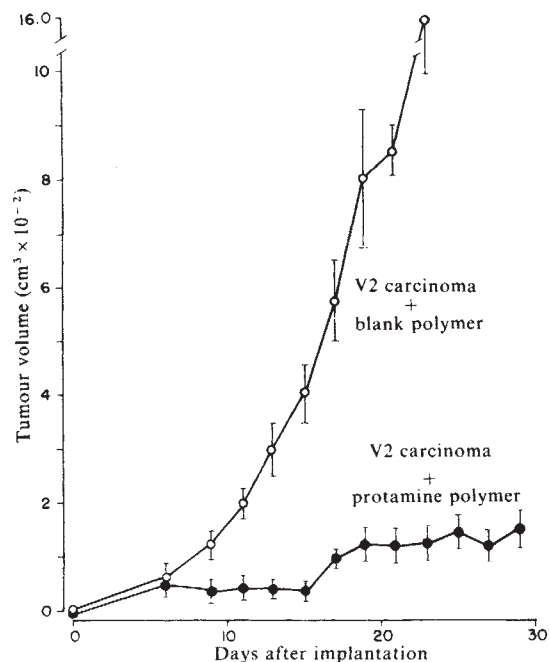
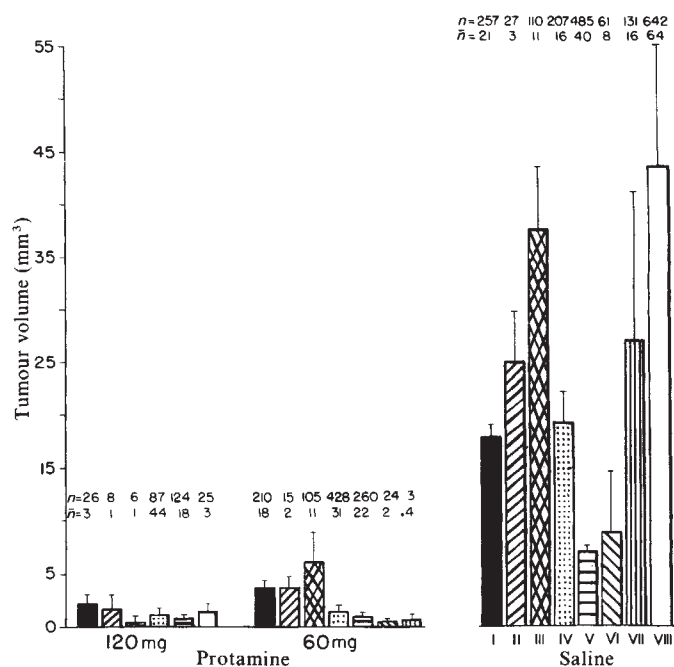


Fig. 5 Inhibition of tumour growth by locally applied protamine when the tumour is implanted directly into the vascular bed. Eight rabbits received a subcutaneous implant of V2 carcinoma in each ear by a method developed by Bronshter *et al.*¹⁵. One ear received two polymer pellets impregnated with protamine as described in Fig. 3 legend. In the opposite ear, two empty polymer pellets were implanted with the tumour. In both ears, tumour growth formed a hemisphere, the dimensions of which were measured with a micrometer caliper. Tumour growth in the protamine-treated pocket (●) was markedly suppressed compared with tumour in the control ear (○). Although capillary growth rate could not be quantified as in the cornea, the extent of vascularization could be observed by transillumination of the ears. The untreated tumours became vascularized on about days 6–7, and rapid growth ensued. In contrast, the protamine-treated tumours generally did not become vascularized, and their growth was slow or undetectable.

Fig. 6 Effect of protamine on pulmonary metastases in mice and rats, ■, Expt I: 36 C57BL/6 male 42-day-old mice received 1.2×10^6 Lewis lung carcinoma cells i.v., and either protamine, 120 or 60 mg per kg, s.c., every 12 h or saline. All mice were killed on day 15. Mice surviving to that day were: 120 mg, 9/12 (3 mice died free of lung metastases on day 2 presumably from a too rapid step-up to the full dose); 60 mg, 12/12; saline, 12/12. The standard error of the differences in means between all groups was significant at $P < 0.001$. In all experiments n = total number of metastases represented by the mean, and $\bar{n}$ = average number of metastases per animal. In this and all subsequent experiments, the mice were weighed twice weekly and the dose of protamine revised upward by increasing the volume according to the average weight of each treatment group except for expts IV and VII where doses were individually calculated. The lungs were fixed in 10% formalin and the lobes separated. The volume and number of metastases were determined with a $\times 12$ stereoscope (eyepiece micrometer 1 unit = 0.064 mm). Two diameters were measured in mm and the volume calculated using the formula³³, $\text{vol} = (d_1 d_2 d_3 \pi) / 6$, where the width of the metastasis is used twice as d_1 and d_2 and the length as d_3 . The measurements were made by two readers on different days who did not know how each specimen was treated. All mice were housed individually. A stock solution of protamine sulphate (Calbiochem) of 10 mg ml^{-1} in saline was warmed to 37°C and filtered ($0.45 \mu\text{m}$ Millipore). The amount of protamine lost in the filter was always less than 4% of the original concentration as measured spectrophotometrically at 230 nm. The protamine solution was stored at 4°C in a sterile 50 ml polyethylene centrifuge tube and warmed to 37°C before use. Treatment began 24 h after tumour inoculation, and only one injection was given on day 1. The twice daily injections began on day 2. Injections were made with a 30-gauge needle in a shaved area over the iliac crest that had been cleaned with a small amount of Betadine solution. Precautions: if one or two doses of protamine are omitted, resumption of the full dose may be highly toxic or lethal. Stepwise resumption to the full dose is necessary. Male mice comfortably tolerated 60 mg per kg, s.c., 12 hourly for 1 yr without signs of toxicity or without showing differences from saline-injected animals. However, at 120 mg per kg 12-hourly, toxicity appeared after 2–3 weeks in 50% of mice. Tumour-bearing mice show less toxicity for a given dose of protamine than do mice without tumours. If a skin ulcer appears, protamine may leak, resulting in non-therapeutic levels of protamine. If a s.c. injection is given too quickly or forcibly, some protamine will enter the venous system and (with doses $> 60 \text{ mg per kg}$) cause sudden toxicity or death. The maximum tolerated single i.v. dose for a mouse is $\sim 6 \text{ mg per kg}$. ■, Expt II: 56 mice received 6×10^5 Lewis lung carcinoma cells i.v., were placed in three treatment groups and killed on day 17. Surviving mice were: 120 mg, 9/25; 60 mg, 10/16; saline, 10/15. Lung metastases were measured in formalin-fixed lungs as described above. In the protamine-treated mice that died before the end of the experiment, the mean volumes of the pulmonary metastases were less than the mean volumes of the metastases in the killed mice. The s.e. of the difference in means of the 60 mg versus saline groups was significant at $P < 0.001$ and that of the 60 mg versus 120 mg groups was significant at $P < 0.05$. ■, Expt III: this experiment was designed to determine the maximum size that could be reached by pulmonary metastases before 50% of the saline-treated host animals had died. Thirty mice received 5.8×10^6 Lewis lung carcinoma cells i.v. and were separated into three groups of 10 mice each. One mouse chosen at random from each protamine group was killed whenever a saline-treated mouse died of tumour, until day 21 when 50% of saline-treated mice had died, and then all the remaining mice were killed. ■, Expt IV: this experiment was designed to determine the effect of protamine on pulmonary metastases shedding from a primary tumour. Seventy-one mice received a s.c. implant (1 mm^3) Lewis lung carcinoma; 25 received protamine, 120 mg per kg every 12 h, 25 received 60 mg and 21 received saline. By day 21 the mean volume of the s.c. primary tumour in the saline-treated mice was $5.4 \pm 0.2 \text{ cm}^3$; it was $2.4 \pm 0.2 \text{ cm}^3$ and $2.9 \pm 0.6 \text{ cm}^3$, respectively, 120 mg and 60 mg groups. All surviving mice were killed on day 24. The survivors were 2/25 in the 120 mg group, 11/25 in the 60 mg group and 7/21 in the saline group. In the protamine-treated mice that died before the end of the experiment, the mean volumes of the pulmonary metastases were less than the mean volumes of the metastases in the killed mice. The s.e. of the difference in means of the 60 mg group versus saline was significant at $P < 0.001$. There was no difference between the 60 mg and 120 mg groups. ■, Expt V: in this repeat of expt IV, 45 mice received s.c. implants of Lewis lung carcinoma and were divided into three groups of 15 mice each. On day 22 the mean volume of the s.c. primary tumour in the saline-treated mice was $6.1 \pm 0.3 \text{ cm}^3$; it was $3.2 \pm 0.2 \text{ cm}^3$ and $2.9 \pm 0.5 \text{ cm}^3$ in the 60 mg and 120 mg groups, respectively. All surviving mice were killed on day 26. The survivors were 7/15, 12/15 and 12/15 for the 120 mg, 60 mg and saline groups, respectively. In the protamine-treated mice that died before the end of the experiment, the mean volumes of the pulmonary metastases were less than the mean volumes of the metastases in the killed mice. The s.e. of the difference in means of the 60 mg group versus saline was significant at $P < 0.001$. There was no significant difference between the 60 mg and the 120 mg groups. ■, Expt VI: this experiment was designed to determine the effect of protamine on pulmonary metastases shedding from a primary tumour which was unresponsive to protamine in the subcutaneous position. Twenty mice received a s.c. inoculation of 10^7 B16 melanoma cells (subcutaneous strain); 12 mice received protamine, 60 mg per kg, s.c., 12 hourly, and 8 received saline. Lung metastases were measured whenever a mouse died. By day 50 three protamine mice and two saline mice were alive and these were killed to end the experiment. The mean volume of the s.c. tumour at the last measurement before death was $14.4 \pm 2.0 \text{ cm}^3$ for saline-treated mice and $11.2 \pm 1.5 \text{ cm}^3$ for protamine-treated mice. The bar graph represents the metastases from all mice. The s.e. of the difference in means between the two groups was significant at $P < 0.001$. ■, Expt VII: a parallel experiment to expt VI except that the primary tumour was responsive to protamine in the subcutaneous position. Sixteen mice received 10^7 B16 melanoma cells (tissue culture strain); 8 mice received protamine, 60 mg per kg 12-hourly, and 8 received saline. Lung metastases were measured whenever a mouse died. By day 50 three mice were alive in each group and they were killed to end the experiment. The mean volume of the s.c. tumour at the last measurement before death was $13.5 \pm 1.0 \text{ cm}^3$ for the saline-treated mice and $0.3 \pm 0.2 \text{ cm}^3$ for the protamine group. The protamine-treated tumours underwent either complete or partial regression, but in this experiment, the protamine dose was not lowered during the regression in order to maintain the dose constant for pulmonary metastases. The s.e. of the difference in means between the two groups was significant at $P < 0.001$. □, Expt VIII: a test of protamine against pulmonary metastases in a different species. Nineteen CD rats (age 21 days) received 5.1×10^6 Walker carcinoma cells i.v.; nine rats received protamine, 120 mg per kg, s.c., every 12 h and 10 received saline. On day 9, 8 of the 10 saline rats died (due to massive pulmonary metastases) and therefore all remaining rats were killed and lung metastases were measured as before except that Bouin's solution was used for fixation. The bar graph represents the mean volume of metastases from all rats. The s.e. of the difference in means between the two groups was significant at $P < 0.001$.



when administered systemically above doses of 60 mg per kg in mice and 120 mg per kg in rats, and this toxicity is unrelated to its angiogenesis-inhibitory activity. This toxicity may severely limit or prevent the clinical use of systemically administered protamine as an antitumour agent. However, in the experimental situations where the appropriate tissue concentration can be achieved, protamine inhibits angiogenesis with the resulting effect on tumours. Furthermore, if the mechanism of the anti-angiogenesis activity of protamine can be determined, this may lead to the discovery of other angiogenesis inhibitors.

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Note added in proof: Female C57BL/6 mice tolerate higher doses of protamine (up to 120 mg) without toxicity.

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LETTERS TO NATURE

Observation of additional low-degree 5-min modes of solar oscillation

Philip H. Scherrer*, John M. Wilcox*,
Jørgen Christensen-Dalsgaard† & Douglas Gough‡

* Institute for Plasma Research, Stanford University, Stanford, California 94305, USA

† National Center for Atmospheric Research, Boulder, Colorado 80307, USA

‡ Institute of Astronomy, Madingley Road, Cambridge CB3 0HA, UK

By measuring the difference between the shifts in the Fe 5,124 spectrum line from light integrated from a central circular portion of the solar disk and from an annular portion exterior to it, we have detected high-order solar oscillations with degrees $l = 3, 4$ and 5. The frequencies of the octupole modes agree well with the values obtained from whole-disk measurements at the South Pole¹. A least-squares fit of the observed frequencies to values interpolated between and extrapolated from the predictions of a sequence of solar models with different chemical compositions selects two models. One of these is almost identical to that obtained by a previous fit¹⁵ of modes with $l \leq 2$, and has a helium abundance somewhat greater than 25% by mass.

Most previous observations of low-degree 5-min solar oscillations have been made with light integrated from the entire solar disk. Claverie *et al.*²⁻⁵ and Grec *et al.*^{1,6,7} have measured spectrum line shifts, and Deubner⁸ and Woodard and Hudson⁹ have measured radiant intensity. Such measurements are most sensitive to modes of degree $l = 0, 1$ and 2; the long continuous Doppler observations made at the South Pole have also isolated octupole modes¹.

Our observations are based on a method used by Severny *et al.*¹⁰. A Babcock solar magnetograph¹¹ at the Stanford Solar Observatory, which is normally used for measuring Zeeman splitting, was converted into an instrument that measures Doppler shifts with equivalent sensitivity. For this purpose one selects a magnetically insensitive Fraunhofer line (with $g = 0$). Light from a central circular area of the solar disk, with radius $0.5 R_{\odot}$, is filtered with a right-hand circular polarizer, and light from the annulus between $0.55 R_{\odot}$ and $0.80 R_{\odot}$ is filtered with a left-hand polarizer. The wavelength difference between the right and left polarized spectrum lines is measured by the magnetograph. It is interpreted, using the Doppler formula, as the difference between the averaged line-of-sight velocities from the circular and annular portions of the solar disk¹².

Because our apparatus convolves the Doppler signal with a function whose length scale is less than the radius $R_{\odot}$ of the solar disk, the degrees of the modes of oscillation to which it is most sensitive are higher than for whole-disk observations.

Our signal should be dominated by modes with $l = 3, 4$ and 5, though contributions from modes with $l = 2, 6, 9$ and 10 should also be detectable¹³. Here we concentrate on the dominant modes.

We obtained good-quality data on 15 days from 17 June to 14 July 1981. The observations were made with 0.1 s time resolution, and were subsequently averaged into 15 s bins. A slow drift, typically of magnitude $1 \text{ ms}^{-1} \text{ h}^{-1}$, was then removed with a high-pass filter. This left data sets over intervals of average duration 9.6 h. Harmonic-amplitude spectra were computed from each data set using a simple least-squares method for finding Fourier coefficients in the frequency range 2.0-4.5 mHz in steps of 1.0 μHz .

Figure 1 shows the average of the 15 spectra. In common with previous observations, power is found to be concentrated between 2.5 and 4.0 mHz, and seems to be generated by a series of oscillators with uniformly spaced frequencies. But whereas whole-disk observations with comparable resolution^{2-4,8} display two peaks per interval of $\sim 136 \mu\text{Hz}$ (corresponding to a mode with $l = 1$ and an unresolved pair with $l = 0$ and $l = 2$), here, as expected, there are three; we infer that they correspond to modes with $l = 3, 4$ and 5.

By selecting every third peak (taking due account of peaks that are obviously missing), one might hope to collect sets of modes of like degree. There are no obvious distinguishing differences between the amplitudes and frequencies of the three sets so obtained, as one would expect theoretically. Therefore we cannot identify the modes using our data alone. It is possible, however, to identify the modes in the data obtained at the South Pole, by comparing the uneven frequency distribution and variable peak heights with theoretical expectations^{1,6,7,13-16}. The frequencies of the modes inferred to have $l = 3$ are indicated by vertical lines in Fig. 1. They can be seen to correspond with some of the peaks of our spectrum.

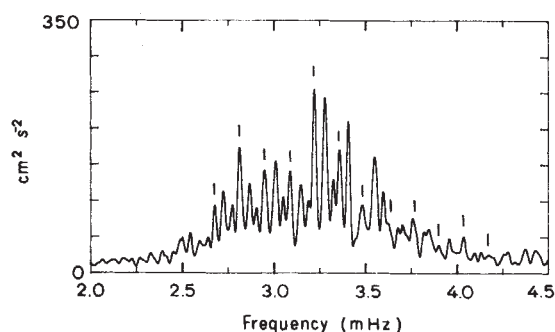


Fig. 1 Average of 15 squared velocity amplitude spectra of data collected in June and July 1981. The vertical lines mark the frequencies of octupole modes measured by Fossat *et al.*¹ at the South Pole.

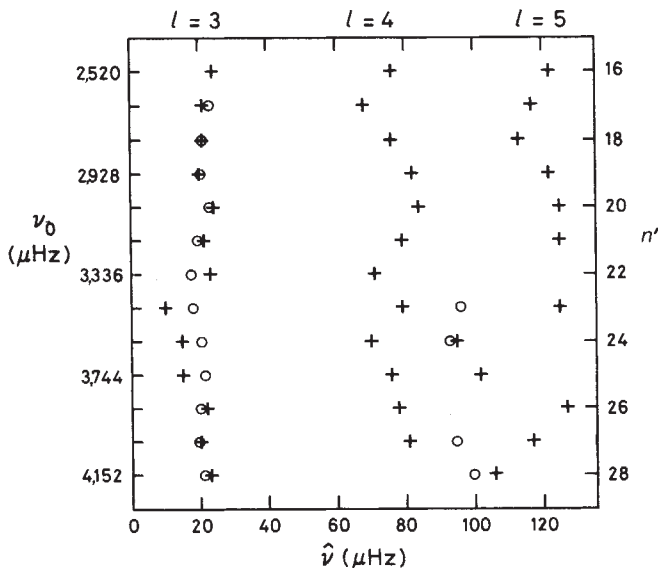


Fig. 2 Echelle diagram of the frequencies between 2.5 and 4.3 mHz of low-degree modes, constructed with $\nu_1 = 72 \mu\text{Hz}$ and $\Delta\nu = 136.0 \mu\text{Hz}$. The frequencies ν of the modes represented in the diagram are given by $\nu = \nu_0 + \hat{\nu}$. +, Frequencies of the peaks in Fig. 1. o, Octupole modes (with $\hat{\nu}$ near $20 \mu\text{Hz}$) and some dipole modes (with $\hat{\nu}$ near $100 \mu\text{Hz}$) observed from the South Pole by Fossat *et al.*¹. Thus by comparing our results with the South Pole data and with theory we identify the degrees of the modes responsible for the three principal columns; these are indicated at the top of the figure. We presume the frequencies 3,703, 3,846 and 4,258 μHz correspond to dipole modes. The ordinate scale n' on the right is the order n or modes with $l \geq 3$, and is $n-1$ when $l=2$. This identification was obtained by the least-squares comparison with theory described in the text. Fitting regression lines $\alpha + \beta(n - n_0)$, with $n_0 = 22 - \frac{1}{2}l$, to the three principal columns of Stanford frequencies ν yields $(\alpha, \beta) = (3,152 \pm 1, 135.7 \pm 0.3)$, $(3,140 \pm 1, 136.2 \pm 0.4)$ and $(3,117 \pm 1, 136.5 \pm 0.3)$ for $l = 3, 4$ and 5 respectively.

To facilitate identification of the modes responsible for our data, we present, following Grec¹⁷, an echelle diagram (Fig. 2) of the frequencies of the peak maxima in Fig. 1. Each frequency ν is reduced to a frequency $\nu_0 + \hat{\nu}$ where ν_0 is an integral multiple of $\Delta\nu$ plus some constant ν_1 , and $\hat{\nu}$ is in the range $(0, \Delta\nu)$. Figure 2 shows a plot of $\nu_0 \equiv \nu - \hat{\nu}$ against $\hat{\nu}$, the spacing $\Delta\nu$ having been chosen to give roughly the same values of $\hat{\nu}$ to modes of like degree. Thus $\Delta\nu$ is representative of the mean frequency differences between modes of adjacent order and like degree. More accurate estimates of these differences are given in the legend.

Included in Fig. 2 are the octupole modes identified in the South Pole data. Because these agree well with one of our columns of frequencies, we deduce that this column also results from octupole modes. The degrees of the new modes producing the other two principal columns are then inferred by comparison with theory¹³. Further comparisons with theory and with other observations will be reported elsewhere¹⁸.

The addition of these new modes to the helioseismological data should impose tighter theoretical constraints on solar models. Here we simply compare the frequencies we have measured with the frequencies ν_A , ν_B , ν_C of the three solar models A, B, C of Christensen-Dalsgaard *et al.*¹⁹ according to the formula

$$\nu_\lambda = \begin{cases} \lambda \nu_A + (1 - \lambda) \nu_B & \lambda > 0 \\ (1 + \lambda) \nu_B - \lambda \nu_C & \lambda < 0 \end{cases} \quad (1)$$

Model A is a standard solar model with initial helium and heavy-element abundances $(Y, Z) = (0.25, 0.02)$; models B and C have initial abundances $(0.19, 0.004)$ and $(0.16, 0.001)$ respectively, and have suffered contamination by heavy ele-

ments in and above the convection zone at a rate chosen to yield a present surface abundance: $Z = 0.02$. The least-squares fit of ν_λ with our frequencies ν represented in Fig. 2 yields $\lambda = -0.29$ and $\lambda = 1.26$ as the two best solutions. The r.m.s. difference between ν_λ and the observations is $\sim 8 \mu\text{Hz}$ for both solutions. The helium-rich solution agrees with that of similar analyses of whole-disk data¹⁵ and low-order modes apparently detected as oscillations in the limb-darkening function²⁰. Therefore we select this as our best estimate. We are then able to infer the orders n of the modes; these are indicated in Fig. 2. Our extrapolated solution has a relatively deep convection zone, and is thus consistent with analyses of 5-min oscillations of high degree^{21,22}.

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Jovimagnetic secular variation

J. E. P. Connerney & M. H. Acuña

NASA/Goddard Space Flight Center, Laboratory for Extraterrestrial Physics, Planetary Magnetospheres Branch, Greenbelt, Maryland 20771, USA

Long-term variations of a planetary magnetic field are one of the few observables available for the study of planetary interiors and dynamo theory. Although variations of the geomagnetic field have been accessible to direct measurement for centuries, knowledge of the secular variations of other planetary dynamos is limited. We report here new limits on jovimagnetic secular variations found by comparison of a jovian internal field model¹ obtained from the Voyager 1 magnetic field observations at epoch 1979.2 with the epoch 1974.9 Pioneer 11 O₄ model². No significant secular variation of either the magnitude or position of the jovidipole was found for the years 1974.9 to 1979.2, although a small Earth-like variation cannot be ruled out.

A gradual decrease in the Earth's dipole moment at a rate of $\sim 5\%$ per 100 yr has been established from observations of the geomagnetic field over the past 150 yr (ref. 3). Less well established but still generally accepted is the slow westward

drift of certain features of the geomagnetic field at a rate of $\sim 0.1^\circ$ or 0.2° long. yr^{-1} . From the palaeomagnetic records it is well known that the Earth's dipole field has a rich history of wanderings and polarity reversals. The irregular and unpredictable switching of the geodipole occurs with varying frequency, a rate of several reversals per Myr being typical of the past 200 Myr.

Geomagnetic secular variations are an important source of information about the Earth's deep interior and the dynamo presumed responsible for the geomagnetic field⁴⁻⁶. Within the context of modern dynamo theory, secular variations can provide constraints on material properties deep within the planet's otherwise inaccessible interior. Comparative studies of planetary dynamos may prove invaluable in unravelling the complexities of the self-sustaining dynamo. Thus the history of Jupiter's planetary magnetic field is of great interest, especially because it represents the first real opportunity to observe secular variations of a planetary dynamo other than the Earth's.

Indirect observations of the jovian magnetic field began with the discovery of non-thermal radio emissions by Burke and Franklin⁷ in 1955 and are still in progress⁸. Continued observations of jovian radio emissions have precisely established the rotation rate of the planet and have suggested the occurrence of secular variations of the jovimagnetic field. Berge⁹ has suggested that the 30% decrease in Jupiter's integrated flux density occurring from 1961 to 1973 may be a result of a decrease in the jovian magnetic dipole moment. An upper limit on the variation of magnetic field strength between epochs 1967 and 1970 of $\sim 5\% \text{ yr}^{-1}$ was obtained from observations of the circular polarization of decimetric radiation¹⁰. From observations of the maximum frequency of jovian decametric radiation, J. K. Alexander (personal communications) concludes that the magnetic field magnitude at high northern latitudes has changed by $< 0.1\% \text{ yr}^{-1}$. Observations relating to the inclination of the jovic dipole with respect to the planet's rotation axis have been interpreted as evidence of a secular decrease of the inclination angle by $0.07 \pm 0.05^\circ \text{ yr}^{-1}$ (ref. 10) but have not been confirmed¹¹.

In situ observations of the jovian planetary magnetic field are limited to the Pioneer 10 and 11 flybys at epochs 1973.9 and 1974.9 and the Voyager 1 and 2 flyby encounters at epochs 1979.2 and 1979.5. Comparison of spherical harmonic models of the jovimagnetic field obtained from the Pioneer observations¹² suggested a decrease in the dipole moment of $\sim 6\%$ during the intervening year. The decrease was, however, attributed to other effects although the possibility of a secular change as large as 6% per year was explicitly not excluded¹³.

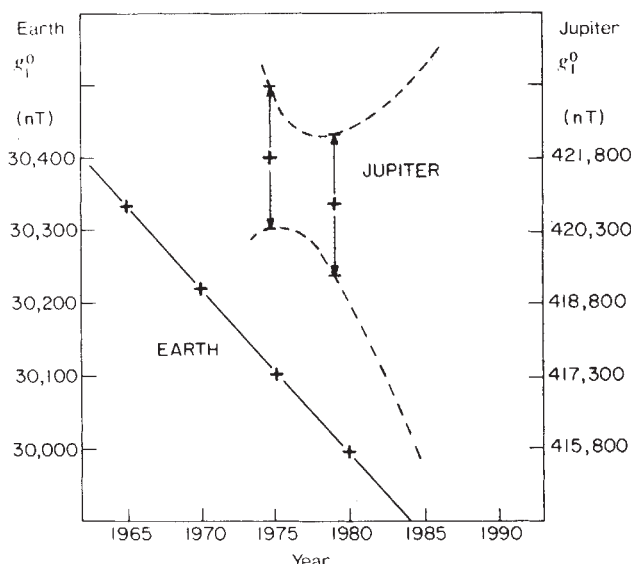


Fig. 1 Secular decrease of the Earth's main dipole g_1^0 term compared with estimates of Jupiter's main dipole term. One vertical division represents $\sim 0.033\%$ of the main dipole term in each case.

Table 1 Jovian magnetic field models

	(1979.2)		(1974.9)		
	V1	P11	P11	P11	
	17 ev*	O ₄ [†]	(2σ) [‡]	15 evs [§]	SHA 23 [§]
	(ε)	(GSFC) [†]	(2σ) [‡]		
1. g_1^0	4.208 (0.032)	4.218 (0.030)	4.068	4.092	
2. g_1^1	-0.660 (0.004)	-0.664 (0.019)	-0.668	-0.705	
3. h_1^1	0.261 (0.005)	0.264 (0.024)	0.243	0.231	
4. g_2^0	-0.034 (0.028)	-0.203 (0.023)	-0.093	-0.033	
5. g_2^1	-0.759 (0.030)	-0.735 (0.039)	-0.672	-0.699	
6. g_2^2	0.483 (0.018)	0.513 (0.048)	0.502	0.537	
7. h_2^1	-0.294 (0.058)	-0.469 (0.037)	-0.498	-0.531	
8. h_2^2	0.107 (0.018)	0.088 (0.037)	0.119	0.074	
9. g_3^0	— (—)	-0.233 (0.060)	-0.111	-0.113	
10. g_3^1	— (—)	-0.076 (0.083)	-0.316	-0.585	
11. g_3^2	0.263 (0.114)	0.168 (0.080)	0.220	0.283	
12. g_3^3	-0.069 (0.054)	-0.231 (0.082)	-0.250	0.067	
13. h_3^1	— (—)	-0.580 (0.104)	-0.476	-0.423	
14. h_3^2	0.695 (0.108)	0.487 (0.108)	0.380	0.120	
15. h_3^3	-0.247 (0.054)	-0.294 (0.068)	-0.228	-0.171	

1965 system III, ϕ positive east unless noted. Schmidt normalized spherical harmonic coefficients, Gauss.

* Ref. 1. † Ref. 2 rotated to 1965 system III. ‡ Ref. 16. § Ref. 12 rotated to 1965 system III.

A preliminary jovimagnetic field model based on Voyager 1 observations¹⁴ yielded a similarly reduced dipole moment attributed not to a secular decrease of the jovian field but rather to the presence of a large-scale current system in the jovian magnetosphere. This azimuthally directed 'magnetodisk' current is confined to an equatorial annular disk extending from $\sim 5R_J$ (jovian radii) to $> 50R_J$ (ref. 15) and appears to be a permanent feature of the voluminous jovian magnetosphere. The relative contribution of this $\sim 3 \times 10^8$ A current system to the magnetic field observed by Voyager 1 near closest approach is greater than that of previous flybys by virtue of the larger periastron of the Voyager 1 encounter ($4.9 R_J$) relative to those of Pioneer 10 and 11 (2.8 and $1.6 R_J$).

A more recent estimate of the jovimagnetic field has been obtained from the Voyager 1 observations¹ through the use of new modelling and inversion techniques¹⁶ which facilitate the separation of externally generated fields from those generated within Jupiter's core. The Schmidt normalized spherical harmonic coefficients of this recent Voyager 1 internal field model are listed in Table 1 along with some previous estimates obtained from the Pioneer 11 vector helium¹² and fluxgate magnetometer observations². The parameters which have no corresponding entry in the V1 list are not determinable from the Voyager 1 magnetic field observations alone and are therefore not available at epoch 1979.2. There is general agreement among the Pioneer 11 and V1 models, and the correspondence between the dipole terms of the V1 and O₄ models is particularly good. Here we consider only a comparison of the V1 and Pioneer 11 O₄ model parameter estimates and the associated estimated parameter uncertainties (in parentheses in Table 1). (Davis and Smith¹³ estimate that uncertainties in the dipole terms of the SHA 23 model quoted in Table 1 are as large as 5% of the g_1^0 term, that is, ~ 0.2 G. They estimate that uncertainties in the quadrupole and octupole terms range from 0.2 to 0.8 G. Since these uncertainties are approximately an order of magnitude greater than those estimated for the O₄ and V1 models we do not consider the SHA 23 model.)

In Fig. 1, the time dependence of the magnitude of the g_1^0 coefficient for both the Earth¹⁷ and Jupiter are compared, scaled such that a major division represents $\sim 0.33\%$ of the field magnitude. A linear fit to the jovian g_1^0 estimates shown in Fig. 1 is

$$g_1^0(t) = 4.218 (\pm 0.015) - 0.0023 (\pm 0.0050)t \quad (1)$$

where g_1^0 is given in G, and t is the time difference in yr from

1974.9. No significant secular variation of the magnitude of the g_1^0 term is found. The observations are consistent with a modest secular increase of $\sim 0.06\%$ yr⁻¹ (at 1 s.d. in the rate) or a decrease of as much as $\sim 0.17\%$ yr⁻¹. For comparison, the observed secular decrease of the magnitude of the Earth's g_1^0 term is $\sim 0.075\%$ yr⁻¹. The dashed lines in Fig. 1 correspond to a 1 s.d. error in an estimate of g_1^0 calculated using equation (1), illustrating the deterioration in predictive capability for epochs far removed from the 1977 median epoch.

A comparison of the two remaining dipole terms g_1^1 and h_1^1 leads to a negligible inferred drift of the magnetic dipole axis of $0.025^\circ (\pm 0.22)$ yr⁻¹ in longitude. The estimated uncertainty in the drift rate is comparable with the uncertainties in Jupiter's rotation rate¹⁸. The inclination of Jupiter's dipole axis has decreased by an insignificant $\sim 0.01^\circ (\pm 0.03)$ yr⁻¹. These conclusions are not substantially altered if an alternative model¹⁶ derived from the Pioneer 11 fluxgate magnetometer observations is used in place of the O_4 model. The uncertainties quoted here are largely the result of uncertainties in the position of the dipole axis at epoch 1974.9. Some of the V1 quadrupole and octupole parameters (in particular the g_2^0 , h_2^1 , g_3^2 and h_3^3 terms) depend on the details of the model used to represent the jovian magnetodisk currents^{1,15} and therefore we will not discuss higher order terms at present.

The *in situ* magnetic field observations are consistent with no secular variation of the jovimagnetic dipole field from 1974.9 to 1979.2. They are also consistent with a modest Earth-like secular variation in both the magnitude of the main dipole g_1^0 term and the drift of the dipole axis in longitude. Earlier suggestions of relatively large secular variations in the dipole moment and inclination¹⁰ are thus not substantiated. Current theoretical estimates of jovimagnetic secular variations based on free hydromagnetic oscillations of the liquid core¹⁹ range from days to centuries. Assuming the Voyager 1 and O_4 models do not represent a chance agreement of two samples of an aliased time sequence, jovimagnetic secular variations must have a time scale of centuries and not decades. It is also clear that the differences in the Pioneer 10 and 11 internal field models reflects more the influence of unmodelled current systems than a real secular variation of the jovimagnetic field. Estimates of the size of Jupiter's conducting core²⁰ based on Hide's method²¹ and the large secular variations inferred from the Pioneer models need to be critically reassessed.

Finally, the methods used to obtain an estimate of the jovian internal field from the Voyager 1 observations¹ should be equally applicable to flybys planned for the near future with similarly large periapses. A similar determination of Jupiter's internal field from either the International Solar Polar Mission (to $\sim 6 R_J$) in 1987 or the Galileo encounter ($\sim 5 R_J$) scheduled for ~ 1990 could in principle distinguish between an Earth-like and no secular variation of Jupiter's main field.

Molecular relaxations in a glass of cholesteric liquid crystal

G. P. Johari*, J. W. Goodby & G. E. Johnson

Bell Laboratories, Murray Hill, New Jersey 07974, USA

Glasses, in which the orientations of molecules have a long-range order, can be obtained by supercooling the mesophases of liquid crystals. Such mesophases may be: (1) nematic, when the centres of their rod-, or lath-like molecules do not lie on a regular lattice, but there is a long-range order in the alignment of their long axes, called the director; (2) cholesteric (or twisted nematic) when the alignment (due to steric asymmetry of the individual molecules) of the nematic type is such that the local director rotates at a steady rate as one moves normal to it; and (3) smectic, when there is also a partial ordering in the positions of the molecules in planes related to the local direction of orientational order. The situation in the nematic and cholesteric phases is clearly akin to magnetic ordering and the glassy states of these phases are useful, as our models of disorder, in understanding the behaviour of structurally isotropic glasses. A study of molecular motions in the glassy cholesteric phase of cholesteryl hydrogen phthalate, given here, shows features which have a striking resemblance to those observed in the (positionally ordered) glass-like state of plastic crystals^{1,2} and the (grossly disordered) molecular and polymeric glasses. This suggests that the characteristic features of the molecular motions in glasses must be explained in terms of the non-equivalence of the molecular environment, rather than in terms of the complexity of the molecule, its internal degrees of freedom, or the state of aggregation. This has implications for our concept of the microstructure of a glass.

Cholesteryl hydrogen phthalate melts to an isotropic liquid at 431 K. The liquid readily supercools and undergoes an isotropic $\rightarrow$ cholesteric transition at 367 K. On further cooling the turbid cholesteric phase becomes increasingly more viscous and undergoes a glass transition at 297 K, as indicated by differential thermal analysis. In the cholesteric phase³ the alignment of the molecular axes has a long-range order as in a nematic phase, but this order is restricted to within the plane and each subsequent plane has molecular orientations (or local director) twisted by an angle of $< 1^\circ$. Thus the arrangement acquires a helical pattern with the optical axis coincident with the helical axis, which is normal to the planes. Measurements were made on unoriented samples contained in a parallel-plate, three-terminal dielectric cell whose temperature was controlled from 77 to 440 K. The distance between the highly polished surfaces of the electrodes was ~ 2 mm and the strength of the electric field was $20\text{--}25$ V cm⁻¹. The cholesteric phase between the electrodes had no preferred orientation; the symmetry of the sample was helical over distances of, say, a few micrometres and spherical over longer distances, because the order induced by the surface of electrodes extends to a distance of a few hundred micrometres, and thus the helical axes for the domains may assume all possible orientations. The capacitance and conductance, or dielectric loss factor, were measured from 0.1 to 100 Hz, using a low-frequency bridge⁴, and from 10^2 to 10^5 Hz, using a GR 1615A capacitance bridge. No change in capacitance or conductance occurred with a change in the electric field strength from 2.5 to 25 V cm⁻¹.

The dielectric loss tangent, $\tan \delta$, at 1 kHz of the supercooled and glassy cholesteric phase is plotted against temperature in Fig. 1. The two peaks are due to molecular relaxations, in the supercooled liquid at 321 K and in the glass at 155 K whose

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* Permanent address: Snow and Ice Division, National Hydrology Research Institute, Ottawa, Canada K1A 0E7.

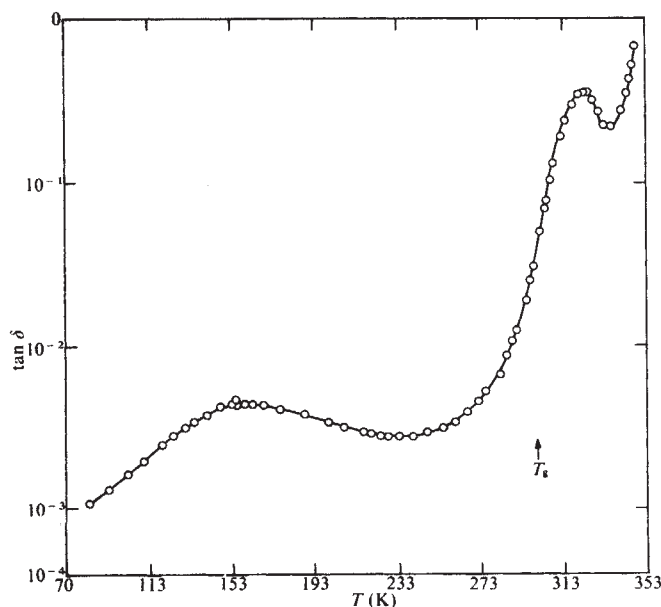


Fig. 1 The dielectric loss factor, $\tan \delta$, at 1 kHz of the unoriented samples of cholesteric phase of cholesteryl hydrogen phthalate in the supercooled liquid and glassy states plotted against temperature. T_g is the calorimetric glass transition temperature.

rates correspond to the frequency of 1 kHz. These are referred to as main and secondary relaxations respectively. The presence of a secondary relaxation indicates that, even in the otherwise rigid matrix of a cholesteric glass, configurational states which involve changes in the electric polarization are available to the structure. The lower magnitude of its dielectric loss, or orientation polarization, also suggests that either the number of molecules contributing to the secondary relaxation and/or the dipole moment associated with the molecular reorientations is much lower than that in the main relaxation.

The spectrum of the main relaxation in a frequency plane is asymmetric and is broader at the high-frequency than at the low-frequency side of the peak. The half-width of the peaks is ~ 2 decades of frequency, which is significantly higher than 1.14 decades characteristic of a single Debye-type relaxation. The spectrum of the secondary relaxation given in Fig. 2 is also broad. Here the half-width of the peaks increases from 4 decades at 190 K to 5 decades at 139 K. Thus both the main and secondary relaxations have a distribution of relaxation times, but the distribution changes significantly with temperature only for the latter. The relaxation rates, which are given by the frequency, f_m , of the peaks in the spectrum, are plotted logarithmically against the reciprocal temperature in Fig. 3. The rate of the main relaxation follows the Vogel-Fulcher-Tamman equation of the type, $f_m = A \exp(-B/(T - T_0))$, where A , B and T_0 are empirical constants. The extrapolated relaxation rate at the calorimetric T_g ($= 297$ K) is 10^{-4} s^{-1} . Thus the molecular degrees of freedom causing the dielectric relaxation of the cholesteric phase are undoubtedly the ones whose freezing out causes the decrease in the heat capacity at T_g . The rate of the secondary relaxation in Fig. 3 follows the Arrhenius equation, $f_m = f_0 \exp(-E/RT)$. This gives an activation energy, E , of 19.8 kJ mol^{-1} for the molecular processes in the cholesteric glass.

The aforementioned features of both the main and secondary relaxations in the cholesteric liquid crystal are strikingly similar to those observed in amorphous polymers^{5,6}, rigid molecular glasses⁷ and orientationally disordered crystals². This similarity suggests that the potential energy barriers resisting the molecular motions, whose freezing out causes the glass transition, are independent of the internal degrees of freedom and the state of aggregation of molecules, and that the molecular mobility is intrinsic to the nature of the glassy state.

In terms of the models for the structure of a glass, which involve dense random packing^{8,9}, microcrystals¹⁰, dislocations¹¹⁻¹⁴, mixed clusters of competing polymorphs^{15,16}, disclinations¹⁷ and dislocations¹⁸, the secondary relaxation may arise from hindered rotations of molecules in localized regions of loose molecular packing¹⁹ (referred to as 'islands of mobility') bounded by the relatively immobile close-packed structures. The localized regions may consist of the interstitial packing²⁰ between the amorphous clusters, or polyhedra, if the structure of a glass consists of regions of varying molecular density. In such a case only a fraction of the total number of molecules in a glass may contribute to its secondary relaxation. Although such localized regions may exist due to the freezing-in of the short range structures corresponding to the density fluctuations in the liquid at T_g , it is also believed that the secondary relaxation indicates small angle movement of each molecule² in the essentially equivalent molecular environments of a dense random packed structure of a glass. In this case all molecules in a glass contribute to the relaxation but each by a small amount.

Owing to the nature of the packing of the rod- or lath-like molecules fewer regions of relatively loose structure would exist in a glass obtained from a cholesteric liquid than in one obtained from an isotropic liquid. Consequently, the magnitude of $\tan \delta$ in the secondary relaxation relative to the main would, in general, be lower in the former than in the latter type of glass. But, if the small angle movement of all molecules were responsible for the secondary relaxation, as is expected in the dense random packed structure of a glass, the aforementioned relative magnitude of $\tan \delta$ would be similar in the two types of glasses. The ratio of maximum $\tan \delta$ at 1 kHz of the secondary to the main relaxation in Fig. 1, is 1:58 in the cholesteric glass, which is much lower than the corresponding ratio of 1:10 or less, observed in most molecular^{2,7} and polymeric glasses⁵. Therefore, the secondary relaxation is likely to be associated with the regions of relatively loose interstitial packing in the structure of a glass.

These results are significant for our understanding of the molecular processes in disordered solids, for it seems that the features of molecular motions in them must have their origins in the non-equivalence of the molecular environment, rather than in the complexity of the molecules, their internal degrees of freedom, or the state of their orientational or positional disorder. The results also support a model for the structure of a glass as an assembly of polyhedra connected by loose interstitial packing, where molecular motion is possible even when the polyhedra are fixed in place. Because supercooled thin

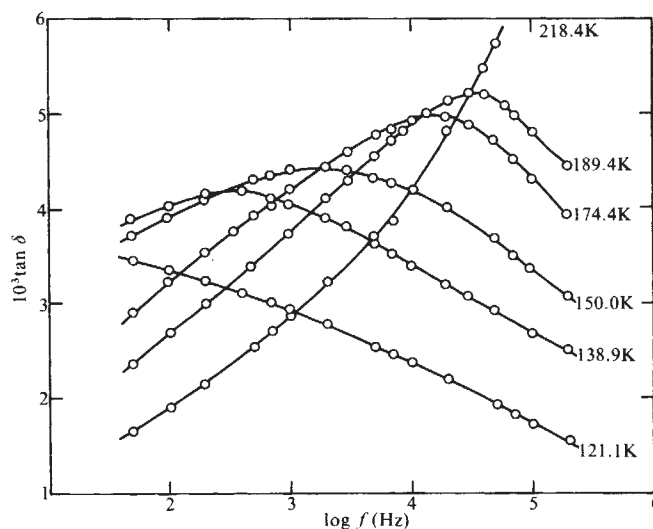


Fig. 2 The dielectric loss factor, $\tan \delta$, plotted against frequency for the secondary relaxation in the glassy cholesteric phase at several temperature.

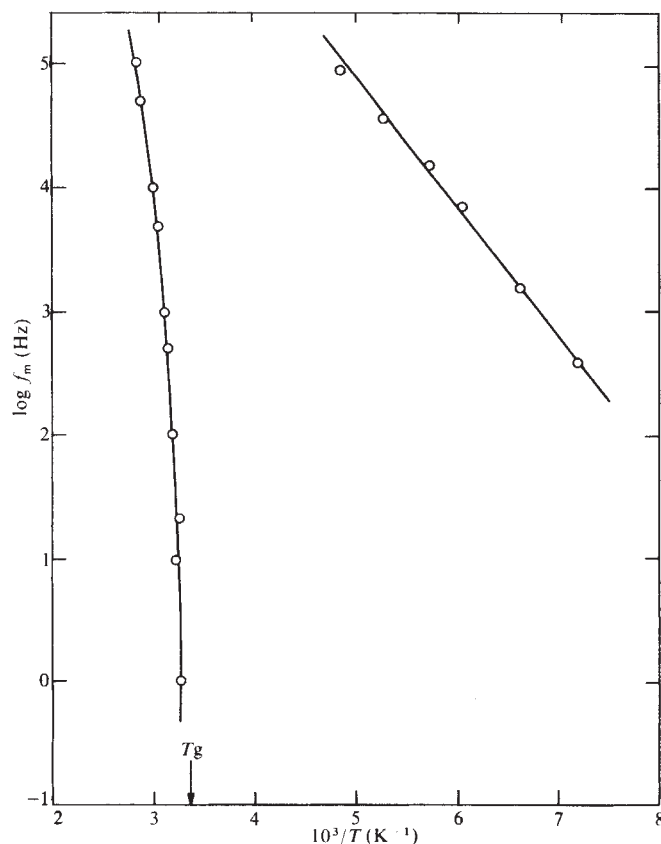


Fig. 3 The frequency of maximum loss, f_m , plotted logarithmically against the reciprocal temperature for main relaxation, and secondary relaxation, in the supercooled and glassy cholesteric phase. T_g is the calorimetric glass transition temperature.

films of cholesteric glass in our experiments are found to be anisotropic, we maintain that the polyhedra in the structure are not microcrystals or crystal nuclei arrested in various stages of their growth, for a random arrangement of such polyhedra would produce a macroscopically isotropic, not anisotropic, structure.

The results have a further implication for our understanding of the glass transition in metal alloys and of the computer simulation of hard sphere glasses, for the configurational restrictions that lead to the formation of a glass in a mesomorphic phase involve mainly the positions (centres of mass) of the molecules and not the orientations or the local director, as no change in the order parameter occurs at T_g . In this respect the glass transition in them is similar to the glass transition in metallic alloys and in the computer simulated experiments on aggregates of hard spheres, where the choice of spheres precludes the possibility of an orientational disorder.

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A 2-D model calculation of atmospheric lifetimes for N_2O , CFC-11 and CFC-12

Malcolm K. W. Ko & Nien Dak Sze

Atmospheric and Environmental Research, Inc.,
840 Memorial Drive, Cambridge, Massachusetts 02139, USA

Accurate values for the atmospheric lifetimes of N_2O , $CFCl_3$ (CFC-11) and CF_2Cl_2 (CFC-12) are vital^{1–3} for studies of their life cycles and in attempts to forecast their future atmospheric levels. These gases are known to be removed mainly by stratospheric photolysis. The lifetimes set by these removal processes are usually inferred from one-dimensional (1-D) models. Using a two-dimensional (2-D) zonal-mean model together with recent observations, we argue here that the stratospheric removal rates may also depend on certain latitudinal features, including latitudinal variations of the gas concentrations, photolysis rates and their correlations, features that cannot be included in the 1-D models. Our discussion also considers the validation of 1-D model results, particularly regarding predictions of atmospheric lifetimes.

The atmospheric lifetime (τ) of a trace gas in steady-state condition can be defined as

$$\tau = \frac{\langle \text{global burden} \rangle}{\langle \text{global removal} \rangle} = \frac{\langle \int fN dv \rangle}{\langle \int LN f dv \rangle} \quad (1)$$

where N is the air number density, f and L are the steady-state volume mixing ratio and loss frequency of the trace gas respectively, and the bracket represents an annual average over time. For gases like CFC-11 and CFC-12 which have not yet attained their steady-state concentrations in the contemporary atmosphere, one may also define a present state lifetime by the ratio of the current burden to current removal rate⁴. This lifetime is in general time dependent and may differ from the steady-state lifetimes defined by equation (1). (Unless stated otherwise, the term 'lifetime' here will refer to the steady-state lifetime.)

The global burden of N_2O , CFC-11 and CFC-12 may often be estimated from the observed concentrations at a few ground stations because the bulk of these gases reside in the troposphere where they are well mixed². The calculation of the global removal rate is, however, less straightforward as it involves the integral of the product of f , L and N . The major contribution to the integral arises from the stratospheric region where the quantities f , L and N vary significantly with altitudes and latitudes. A common approach is to approximate the integral (which may be interpreted as a spatial and temporal average of the product) by the product of the corresponding averaged quantities. This approach clearly ignores the correlation between the quantities f , L and N and hence its contribution to the integral. The neglect of this correlation may introduce significant errors^{5,6} in the calculation of certain reaction rates. We now show that the global removal rate depends not only on the vertical structure of f , L and N in the stratosphere, but also on their latitudinal distributions and correlations.

Three approaches are used to determine the atmospheric lifetimes of the above gases. The first requires empirical knowledge of the source strength and burden. The second approach is to calculate the global removal rate in equation (1) with the spatial distribution of f constructed from available field data, an approach used by Johnston *et al.*⁷ in their analysis of N_2O budget. The limitation of these two approaches is that an extensive set of global data is often needed.

In the absence of sufficient data coverage, one must resort to the third approach which uses models to calculate f and τ while using the limited amount of observations to validate the computed gas distributions. A favourable comparison between calculated and observed f may be used as support for the predicted lifetime.

Among the hierarchy of models, the 1-D models are most

widely used^{1,2}. The problems with 1-D models concern the interpretation of their simulated vertical profiles which are considered to represent some sort of global longitudinal and latitudinal averages. Strictly, 1-D model results should be compared with the observed global averages defined by a large set

of spatial and temporal data. Acquisition of such a data set for any trace gas is clearly an enormous task. Even if such global data are available, difficulty still remains in the assessment of the 1-D model predicted lifetimes. Specifically, the global removal rate calculated using the 1-D vertical profiles of f , L and N may still be in error due to the neglect of the zonal and latitudinal correlation between f and L even if the calculated profiles agree with globally averaged observations.

Recent data on N_2O , CFC-11 and CFC-12 (refs 8–14) show that at each given altitude above tropopause, higher concentrations are always found in the tropical stratosphere, a region where the solar UV radiation which dissociates the gases is most intense. Thus, the contribution from the covariance of f and L to the global removal rate could be significant. To account for the covariant effect, multi-dimensional models are needed.

Ideally, a three-dimensional (3-D) model should be used in the lifetime calculation as the spatial and temporal correlations between different quantities (such as L and f) appearing in equation (1) can be properly treated in the integrals. A 3-D study for N_2O has been made by Levy *et al.*¹⁵. The main disadvantage of using a 3-D model is that it uses a lot of computer time.

The distribution of f calculated from the 2-D zonal-mean model is representative of the zonal average concentrations. If one assumes that the zonal deviation of f is small, the global removal rate can be accurately approximated by integrating the product of the zonal-mean f and zonal-mean L . This assumption is supported by 3-D model simulation of the N_2O distribution¹⁵, and seems to be appropriate for CFC-11 and CFC-12. We shall now use a 2-D model to demonstrate that the latitudinal covariance often exists and may not be negligible for gases such as N_2O , CFC-11 and CFC-12.

Figure 1 shows the N_2O observations^{8–14} at different latitudes together with profiles from our 2-D model¹⁶. Both the data and the model reveal significant vertical as well as latitudinal variations in the N_2O mixing ratio. The overall agreement between model and observation is good.

Figure 2 shows the model calculated column removal rate of N_2O as a function of time and latitude. Note the strong latitudinal gradient, a feature reflecting the important effect of the latitudinal variations in local concentration and local solar flux. During spring and autumn, the maxima occur around the Equator, whereas during summer and winter, they occur about 15° above and below the Equator respectively. Our calculation shows that the net contribution to the global removal rate from the covariance of f and L is positive. The annual average column removal rate for N_2O is 1.2×10^9 molecules $cm^{-2} s^{-1}$. With a calculated column abundance of 6×10^{18} molecules cm^{-2} , a lifetime of 159 yr is derived. This value may be compared with values of 175 and 150 yr calculated by Johnston *et al.*⁷ and Levy *et al.*¹⁵ respectively.

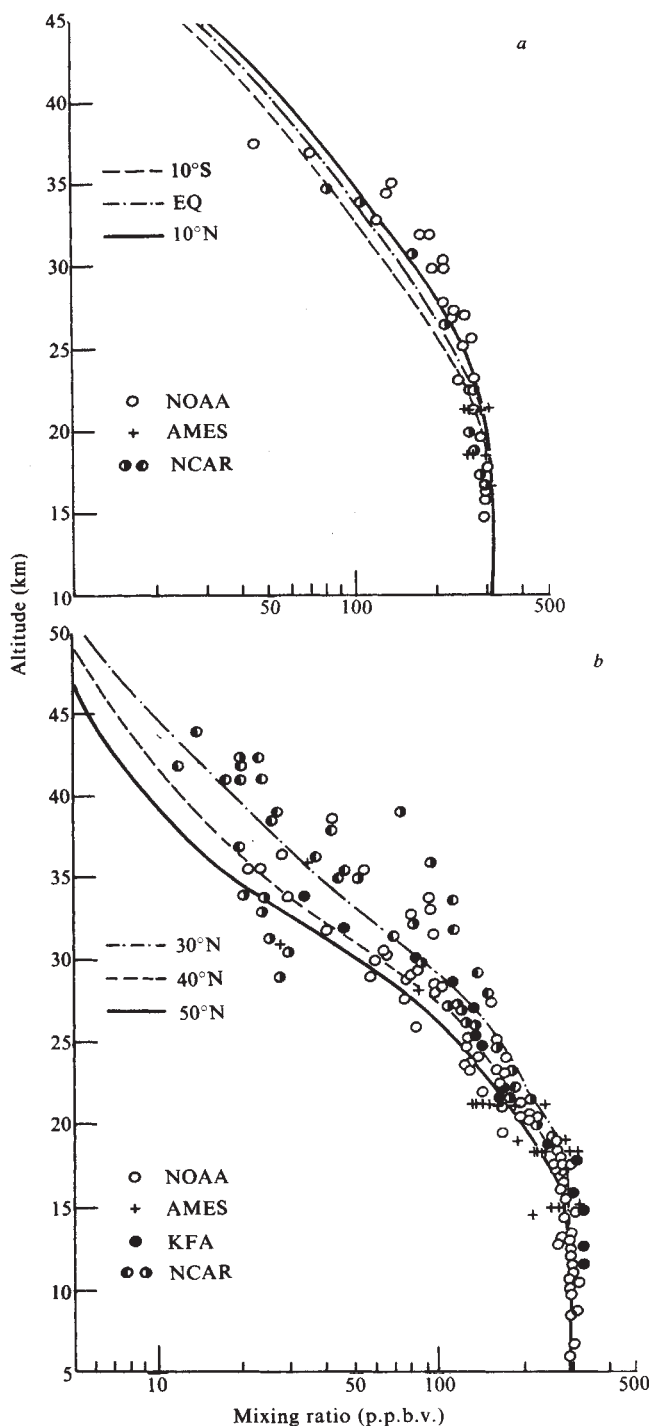


Fig. 1 Calculated N_2O profiles together with observations for equatorial (a) and mid-latitude (b) regions. The profiles are calculated using the 2-D zonal-mean model described in ref. 16. Dynamic transports in the model are simulated by advection from zonal-mean wind plus eddy transport parameterized by a symmetric eddy diffusion tensor. The wind fields are from ref. 20, while the values of the eddy diffusion tensor are from ref. 21. The reaction rates are from the NASA-WMO Workshop recommendations¹⁸. A temperature-dependent absorption cross-section²² is used to calculate the N_2O photolysis rate. A uniform boundary value of 300 p.p.b.v. at the ground is assumed for the calculation. The data shown are reported by groups from NOAA^{8,9}, NASA-Ames^{10–12}, KFA¹³ and NCAR¹⁴.

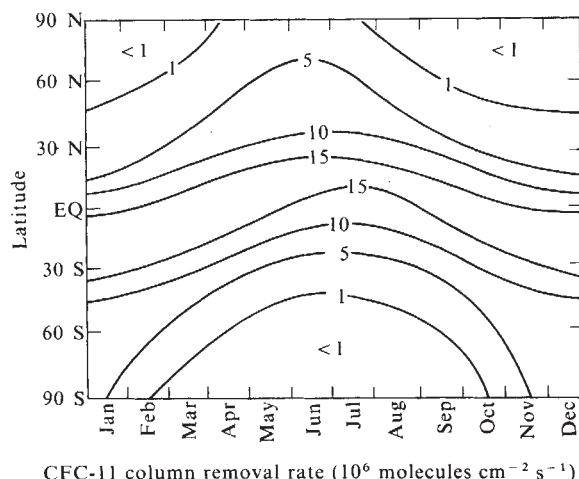


Fig. 2 Calculated N_2O column removal rate as a function of latitude and time of the year.

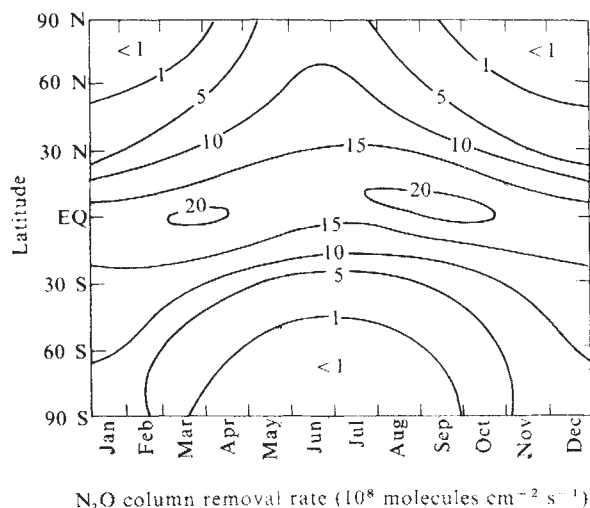


Fig. 3 Calculated CFC-11 column removal rate as a function of latitude and time of the year. The model simulation was performed using a boundary value of 1 p.p.b.v. at the ground.

We have also calculated the lifetimes for CFC-11 and CFC-12 using a steady-state simulation. Direct comparison of the calculated gas distributions of this model simulation with observations is not possible as the gases have not attained the steady-state concentrations in the present atmosphere. As an alternative, the computed CFC-11 and CFC-12 distributions corresponding to the year 1979 of a model simulation using known release rates¹⁷ can be compared with the available observations⁹⁻¹⁴. Agreement is reasonably good for CFC-11 and CFC-12 at the Equator but poor at mid-latitudes¹⁸. The calculated mid-latitude CFC-11 and CFC-12 mixing ratios above 25 km are higher than the observations by about a factor of 2-4. The discrepancy could be due to either the error in the photolysis rates or error in the transport coefficients. The column removal rate of CFC-12 has features very similar to that of N₂O (Fig. 2). For CFC-11, the latitudinal gradient of the removal rate is stronger as shown in Fig. 3. The calculated lifetimes are 65 and 135 yr for CFC-11 and CFC-12 respectively.

The corresponding 2-D model calculated lifetimes reported by Hinds¹⁹ are 81 and 182 yr and those from the Oxford University model³ are 78 and 133 yr respectively. Direct comparison of these values with our calculated values is difficult because it is not clear whether the values reported correspond to steady-state lifetimes.

Note that the calculated lifetimes given here also depend on model structure, such as parameterization for transport and treatment of photochemistry. The question of whether these calculated values truly represent the actual atmospheric lifetimes can be answered only following further validation of the corresponding calculated distributions using more observational data and improvement in transport and chemical data. However, we believe that the latitudinal behaviour of the column removal rate simulated by the 2-D model is qualitatively correct and that the positive correlation between the latitudinal variation of f and L should not be ignored.

Although 1-D models are still the most widely used diagnostic and prognostic tools in stratospheric research, two limitations should be noted with regard to their lifetime predictions: first, their inability to incorporate the covariance effects discussed here; second, and more problematic, the inherent difficulty in validating their lifetime predictions using field data. Our discussion points to the fact that, even for a fully validated 1-D model in which the calculated profiles agree with global average observations, the model may still underestimate the global removal rate and, therefore, overestimate the lifetime because of its inability to account for the positive contribution from the covariance of f and L . With a modest increase in computer time, 2-D models, on the other hand, can simulate the latitudinal and seasonal variations of atmospheric species as

well as the solar insolation and may therefore be useful in refining the lifetime estimates calculated by 1-D models. In light of the above discussion, a combination of selective field data and a validated 2-D model appears to be the best approach to obtaining more accurate lifetime estimates. Obviously, 2-D models are still in a developmental state, and more atmospheric data are needed for further validation and improvement.

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Position of the Lhasa block, South Tibet, during the late Cretaceous

Jean-Pierre Pozzi*, Michel Westphal†, Yao Xiu Zhou‡, Li Sheng Xing‡ & Xian Yao Chen‡

* Institut de Physique du Globe de Paris, 4 Place Jussieu, F-75230 Paris Cedex 05, France

† Institut de Physique du Globe de Strasbourg, 5 rue Descartes, F-67084 Strasbourg Cedex, France

‡ Chinese Academy of Geological Sciences, Bai Wan Zhuang Road, Beijing, People's Republic of China

The latitude of the Lhasa block (Xizang, South Tibet) during the late Cretaceous-early Tertiary is of prime importance for understanding the collision of India and Eurasia and the mechanism of the formation of the Qinghai-Xizang plateau. During the first field expedition of the French-Chinese collaboration, several geological formations have been sampled in southern Tibet between Lhasa (29.40° N; 91.09° E) and Dingri (28.35° N; 86.38° E). We present here the first results obtained for middle Cretaceous to Palaeocene red beds from the Lhasa block, north of the Yarlung-Zang Bo suture zone, recognized as the main suture between the Indian and the Eurasian plates. They indicate a palaeolatitude of the Lhasa block of 20° N during the late Cretaceous while India was situated 30° S.

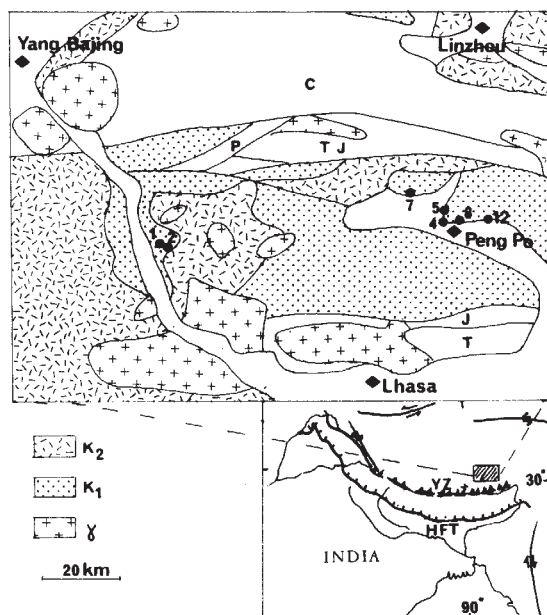


Fig. 1 Geological outlines of the Lhasa region: C, Carboniferous; P, Permian; T, Trias; J, Jurassic. K₁, Takena Formation and lower-middle Cretaceous; K₂, Lingzizong Formation; γ, granitic intrusives. Redrawn from geological map of Lhasa-Nyalam Area (Academia Sinica). YZ, Yarlung Zang Bo suture zone; HFT, Himalayan Frontal Thrust.

The geological formations that we sampled were red beds from Linzhou basin. Continental sediments are present all over the Tibetan plateau and particularly in the Linzhou basin north-east of Lhasa (Fig. 1) where they are represented by two formations separated by a major unconformity. The rock lying under the unconformity is Takena Formation of middle to late Cretaceous age, mainly consisting of sandstone, limestone and shale, strongly folded and with a total thickness of ~1 km. Volcanics (andesite and dacite) are interbedded at the base of this formation. Above the unconformity, Lingzizong Formation of late Cretaceous age mainly consists of black shale in its lower part and red sandstone often conglomerate upwards. A thick sequence of greyish-blue andesite overlays the Lingzizong Formation. Red sandstones of the Takena Formation were sampled (Fig. 1) at sites 1, 2, along the road Lhasa-Yangbajing and at sites 4, 5, 7, 8, 12 near Linzhou (Peng Po Farm).

Samples were taken with a portable drill or as block samples, and were oriented with magnetic and solar compass. Individual

sites were sampled laterally over 50–100 m and vertically over 10–20 m.

The measurements were done in Paris and Strasbourg on standard 25-mm cores using either a Schönstedt or a Digico Spinner magnetometer. The two series of measures were cross checked. Samples were demagnetized by step heating and cooling in a zero field (better than 20 nT). The different magnetic components were analysed using the classical Zijderveld vector diagram method.

Thermal cleaning shows the presence of two magnetic components in approximately half of the samples. One is eliminated after heating at 400–500 °C and does not show a clear mean direction. The other is only broken down above 650 °C and is usually the last component. The directions of this component are well grouped. Other samples show only one direction eliminated above 650 °C. Before tectonic correction, the mean directions are generally different from the present field.

Table 1 shows the results before and after tectonic corrections. *k* increases from 7.3 to 35 by a factor of 4.8. Statistical tests have been used to estimate the validity of the fold test. McElhinny's test¹, which is very stringent, is positive at 95% significance level. McFadden and Jones² devised another test but this was difficult to use when each site had a different tectonic setting. We can confidently conclude that the fold test is positive and that the magnetization predates the late Cretaceous–Palaeocene folding phase.

In site 7, four specimens are of normal polarity while seven are inverse, the two directions being antiparallel. The presence of normal and reverse polarity in site 7 of red and green sandstone also argue for a primary origin of the hard component of magnetization.

Nevertheless, against the strong technical arguments for primary origin, one has to consider (Fig. 2) that before bedding correction, the virtual geomagnetic poles (VGP) for sites 1, 2, 4, 5, 8 and 12 are not significantly different (C. T. Klotwijk, personal communication) from the apparent polar wander path (APWP) for India. In the Linzhou basin, tectonic movements of comparatively little amplitude occurred after the main late Cretaceous–early Tertiary folding phase. VGP from site 7 with

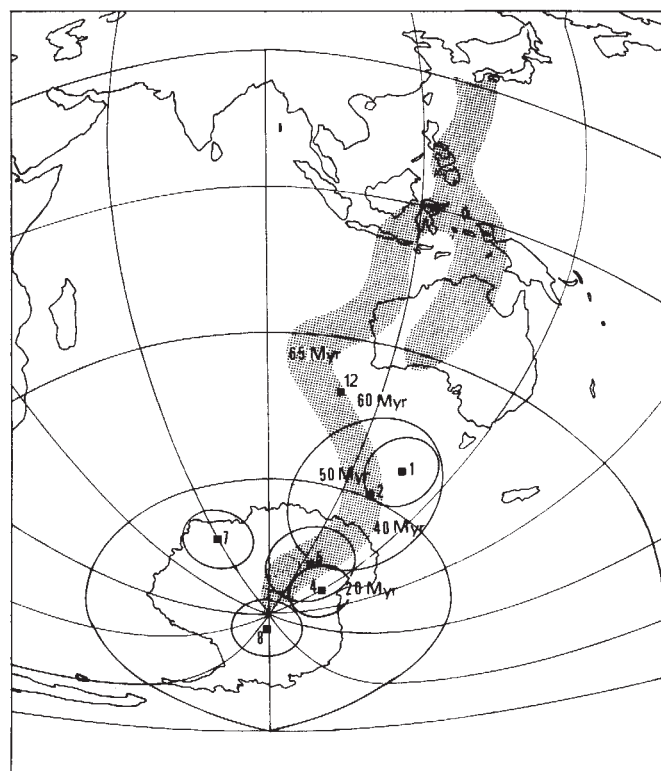


Fig. 2 APWP for India (from ref. 6) compared with the geomagnetic poles of Cretaceous Tibetan sediments and volcanics before unfolding.

Table 1 Palaeogeomagnetic results before and after tectonic correction

Present results							
Site	Before unfolding			After unfolding			α_{95}
	N	D	I	D	I	k	
1	8	335	2	324	37	68	7°
2	7	341	9	333	43	16	16°
4	9	350	42	333	28	90	5°
5	10	352	33	328	47	36	8°
7*	11	10	25	3	24	69	6°
8	11	0	52	338	29	51	6°
12	12	344	-33	341	42	48	6°
Mean before tectonic correction		350	20	—	—	7.3	24
After tectonic correction		—	—	338	36	35	10
Mean PGV: N = 7 sites Lat. 68° N Long. 340° E							
Palaeolatitude for Lhasa 20° N							
Previous results ^{3,4}							
Red beds (Linzhou)							
Zhu Xiang Yuan	12	—	—	335	16	66	5°
Zhu Zhi Wen	42	—	—	338	40	20	7°
Lhasa Upper Jurassic	21	—	—	175	2	5	17°

* Both reverse and normal samples.

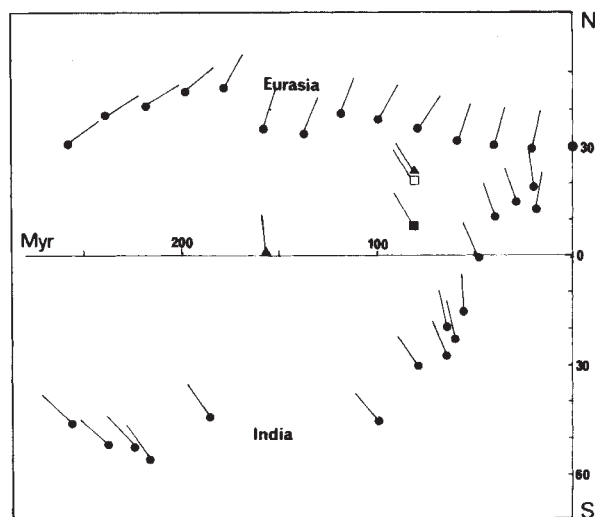


Fig. 3 Palaeolatitude and palaeorientation of a point now in Lhasa as if it were bound to Eurasia (upper curve), or as if it were bound to India (lower curve). Recalculated from ref. 5 and from refs 6, 7. □, Results from this paper; ▲, results from ref. 4; ■, results from ref. 3.

both normal and reverse layers is different from the APWP of India. Although only a few sites are considered here, it seems that VGP's from site 12, from sites 1 and 2 and from sites 4 and 5 correspond respectively to periods of 65, 50 and 25 Myr on the APWP for India, the two last being critical periods for remagnetization. This could argue for a remagnetization of these formations, when the Lhasa block collided with India. If remagnetization occurred, other methods of investigations will be necessary to decipher the magnetization, or other types of formations should be used to assess the palaeolatitude of Lhasa block; useful conclusions can then be deduced from overprinted components concerning the latitude of the collisions, but it will be difficult to explain how three phases of remagnetization have affected, first site 12, then sites 1 and 2 and possibly sites 4, 5 at 65–50 Myr in a near equatorial latitude, and finally at higher latitude site 4, at 25 Myr.

Until now, the positive fold test has led us to conclude that a complete remagnetization probably did not occur and that the results give a good approximation of the position of the Lhasa block during the Cretaceous.

Chinese palaeomagnetists have done several studies in Xizang, only a few of which have been published. Zhu Xiang Yuan *et al.*³ have sampled the Takena red beds probably not far from site 4 (the Yayong hill near Peng Po farm). A few samples were a.f. demagnetized up to 30 mT and do not show any directional change. The result given is based on natural remanent magnetism measurements and is dip corrected.

A more extensive study has been published by Zhu Zhi Wen *et al.*⁴ over Xizang. Results concerning the Lhasa block are on red beds from Takena (Lhasa cement mill). All samples were a.f. demagnetized up to 50 mT and the results corrected for tilt are given in Table 1.

Compared with the Chinese results for the Linzhou red beds, new results have been obtained on more widely distributed sites using thermal demagnetization techniques which are generally more effective for resolving multi-component magnetizations of red beds than are a.f. techniques. Indeed, a.f. demagnetizations performed on red beds by Zhu Zhi Wen and others leave 90% of the initial magnetization undestroyed at the peak field used (50 mT).

Figure 3 gives the palaeolatitude of Eurasia recalculated from ref. 5 and India from refs 6, 7 as a function of time, with the results of Zhu Zhi Wen⁴ for Jurassic limestone and Cretaceous red beds. Arrows indicate declinations with respect to the north and show an anticlockwise rotation of the Lhasa block since the Jurassic. During the middle Cretaceous, the palaeolatitude of the Lhasa block was about 20° N. The results of Zhu Zhi

Wen⁴ indicate a near equatorial latitude during the Jurassic. These results confirm that the Lhasa block, which is of Gondwanan origin and has preceded northwards drifting India, was widely separated from India during the late Cretaceous and possibly during the Jurassic according to Zhu Zhi Wen results (Fig. 3). During the Cretaceous the northern edge of India was situated near 30° S and the southern margin of Asia probably not far from 30° N. As the palaeolatitude of the Lhasa block was about 20° N it is likely that the Tertiary convergence between South Tibet and India was much larger due to subduction and crustal shortening⁸ than between South Tibet and Asia. The anticlockwise rotation of the Lhasa block (Fig. 3) probably occurred under the constraint of the anticlockwise rotation of northward moving India block.

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Palaeoclimates at Lake Turkana, Kenya, from oxygen isotope ratios of gastropod shells

Paul I. Abell

Chemistry Department, University of Rhode Island, Kingston, Rhode Island 02881, USA

Climatic changes in the Plio-Pleistocene of East Africa during the evolutionary development of early man have been identified only in their broadest outlines. A variety of palaeontological^{1–3} and geochemical⁴ techniques have already been applied to the study of palaeoclimates in this area, but the use of stable oxygen isotope ratios, so helpful in marine palaeoclimatology, has not been fully exploited^{5,6}. The frequent occurrence of well-preserved mollusc shells in the sedimentary column at Lake Turkana provides a sensitive oxygen isotope record, varying over a range of 7‰, which can be interpreted in terms of evaporative concentration of the heavier oxygen isotope in waters of the closed lake, alternating with isotopically lighter freshwater when the lake has been open. I report here the results of a study of the ¹⁸O/¹⁶O ratios of three species of gastropods from the sediments of the Koobi Fora region of Lake Turkana, and evaluate how the technique might be applied to the study of the palaeoclimates of other tropical lakes.

The sedimentary deposits of palaeo-Lake Turkana in northern Kenya are well known for their yield of hominid fossils⁷ and artefacts⁸ of early man. They also include numerous and varied land and freshwater fossils, including the frequent occurrence of well-preserved mollusc shells. A well-documented collection of these shells⁹ provided the impetus and raw materials for this study. Among the 95 shell-bearing horizons recognized by Williamson in his study of the palaeontology of the Lake Turkana molluscs, some 36 contain the gastropods *Mellanoides tuberculata*, *Cleopatra ferruginea* and *Bellamya unicolor*. These three were chosen from among the ~20 species identified by Williamson because: (1) they occur in shallow water habitats and would be expected to be in good equilibrium with the surrounding water; (2) they are capable of living over a wide range of pH and concentrations of dissolved salts

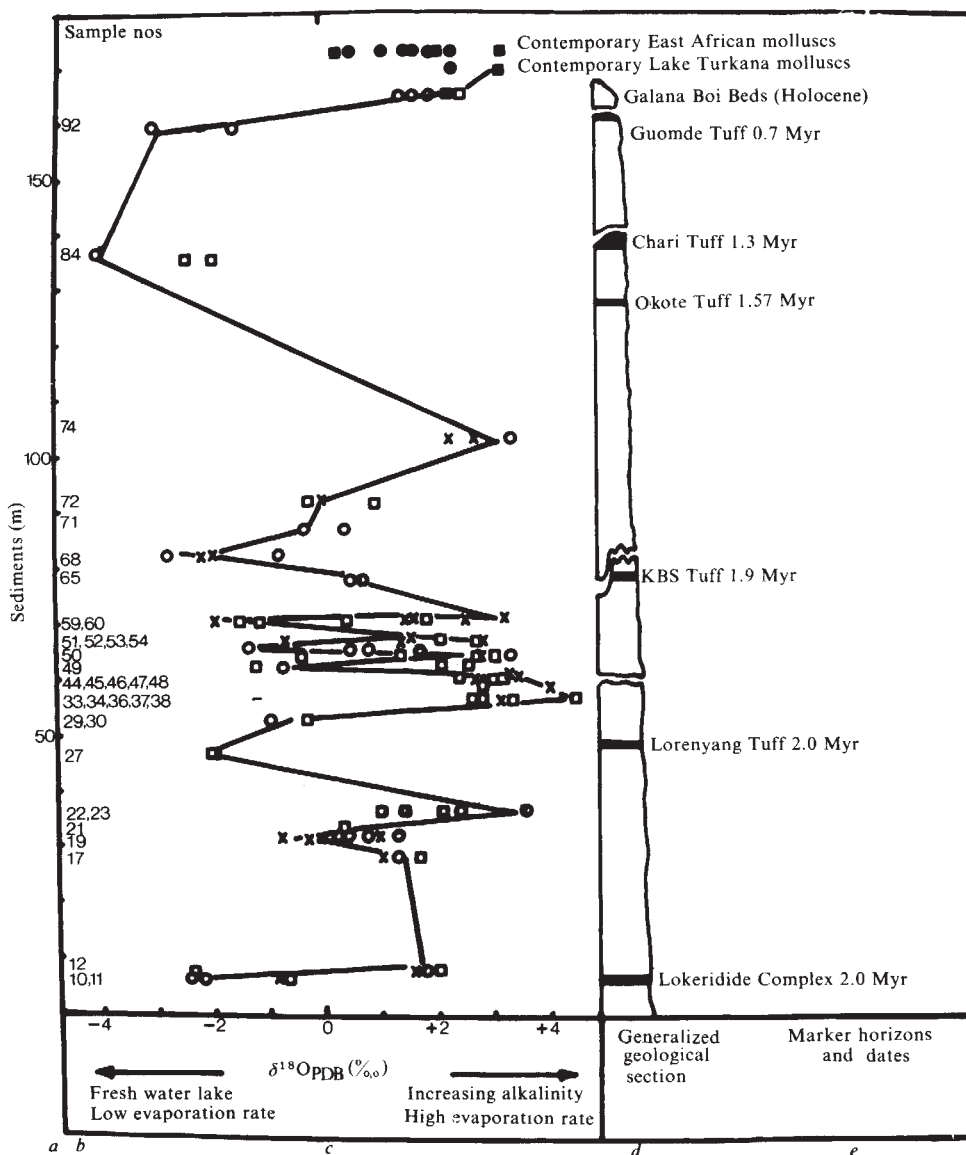


Fig. 1 Variation of $\delta^{18}\text{O}_{\text{PDB}}$ with stratigraphical level of the fossil molluscs in the Plio-Pleistocene sediments east of Lake Turkana, Kenya. *a*, Sediment depth. *b*, Molluscan stratigraphical levels. These levels were assigned by Williamson³ and are numbered consecutively from the lowest and oldest horizon where shells are found, upwards. The stratigraphical levels cited include all those in which one or more of the three species of gastropods chosen for this study were found. *c*, $\delta^{18}\text{O}$ in ‰ versus the PDB standard. $\times$, Fossil *Cleopatra ferruginea*; $\square$, fossil *Bellamyia unicolor*; $\circ$, fossil *Melanoides tuberculata*, all from the Lake Turkana sediments; $\blacksquare$, contemporary *Bellamyia*; $\bullet$, contemporary *Melanoides*. In constructing the regression line, generally the most extreme values of $\delta^{18}\text{O}$ at each level were selected, representing the extremes of evaporative concentration of H_2^{18}O , or dilution by meteoric water. This emphasizes short-term extremes of climate over longer-term averages. *d*, Generalized geological section, with disconformities. *e*, Dated marker beds. The contemporary Lake Turkana gastropods came from delta areas near the Omo and Kerio Rivers. The stratigraphy and tuff marker bed correlations are described elsewhere^{11,19,20}. Reproducibility for the isotope measurements was $\pm 0.1\%$ for multiple analyses of the same individual gastropod and generally better than $\pm 0.5\%$ for interspecies comparisons when more than one species was found at the same stratigraphical level.

(although *Bellamyia* is more sensitive than the other two); (3) they frequently inhabit the same sedimentary horizon, and thus provide an intergeneric check on the isotope results; and (4) they are the most ubiquitous of the Lake Turkana molluscs, and are thus best suited to give a reasonably continuous climatic record.

Well-preserved specimens were selected and whole shells were ground to a powder and examined by X-ray diffraction for aragonite/calcite ratios. All results reported here are for shells of $>90\%$ aragonite. Oxygen isotope ratio measurements were made on a VG Micromass 602C spectrometer, the $\delta^{18}\text{O}$ values were calculated in the usual way and are reported here versus the PDB standard¹⁰. The results are shown in Fig. 1, together with various stratigraphical and sampling data. Details of collection sites, stratigraphy and palaeontology are given elsewhere^{3,9,11}, while locations and the sample numbers used in this study are recorded in Fig. 2. The results from the Williamson collection were supplemented by a few samples which I collected from the Galana Boi Beds (Holocene), and samples from the modern lake, obtained by dredging near the mouths of the Kerio and Omo Rivers. For comparison contemporary gastropod shells from Lakes Victoria, Edward, Albert and Kivu were analysed and their isotopic results included at the top of Fig. 1. Excursions of the oxygen isotope curve towards positive values represent evaporative regimes and indicate dry and/or hot climates. Excursions towards negative values represent non-evaporative conditions, and indicate cool and/or wet climates.

Note that a few of the climatic fluctuations in Fig. 1 are marked by a substantial range of isotopic values at the same stratigraphic horizon (for example, 59, 60), implying a substantial change in $\delta^{18}\text{O}$ with little change in lake level. A rapidly changing microenvironment is the obvious explanation, but no choice can be made among the many detailed scenarios that might produce such changes. These situations are, fortunately, few in number, and do not vitiate the principal trends.

The concentration of the heavier isotope of oxygen in evaporative regimes is well known^{12,13} and has been studied over short time spans in both marine and lacustrine environments. The study by Fontes and Gonfiantini¹⁴ on Saharan closed basins, Gara Diba Guelta and Melah Sebkh, is the most pertinent. However, the nearly idealized conditions of their study (limited to 1 yr on a basin with no further input of water or salts during that year) are difficult to extrapolate to Lake Turkana, which has existed for 10,000 yr as a closed basin since its last flushing¹⁵, has had continuous but erratic input of water during that period, and been through a period of considerable volcanic activity by volcanoes actually in the lake, and has been subjected to widely different conditions of relative humidity during those years. Nevertheless, at Lake Turkana, the evaporative history can be deduced approximately because we have three known points defining the relationship between $\delta^{18}\text{O}$ and the increasing alkalinity of the lake. This relationship is shown graphically in Fig. 3. In temperate cool/wet climatic conditions, calcium carbonate precipitated from meteoric water has a range of $\delta^{18}\text{O}_{\text{PDB}}$ at about -5 to -4% (ref. 16), depending on the

prevailing temperature¹⁷. (A 5 °C temperature range, such as currently exists among East African lakes¹⁸, is indicated by the crosshatched area of Fig. 3.) At Lake Turkana, the most positive $\delta^{18}\text{O}_{\text{PDB}}$ values for mollusc shells fall near +4‰, representing near extinction conditions (16 mequiv. l^{-1} of alkalinity). The present lake, with virtually all molluscs extinct except in areas immediately off the mouths of the Omo, Turkwell and Kerio Rivers, has an alkalinity of 22 mequiv. l^{-1} and a $\delta^{18}\text{O}_{\text{SMOW}}$ value of +6‰, would be expected to precipitate calcium carbonate with a $\delta^{18}\text{O}_{\text{PDB}}$ value of nearly 6‰ (ref. 16). Note that Fig. 3 is an approximation for palaeo Lake Turkana only, and a line of drastically different slope could result from similar constructions for other lakes, or even for Lake Turkana in different carbonate supply conditions. (Lake Baringo, $\delta^{18}\text{O}_{\text{SMOW}} = +8.43\%$ and an alkalinity of 4.44 mequiv. l^{-1} (ref. 16) represents such a very different lake.)

A similar alkalinity-oxygen isotope curve can be constructed for other palaeolakes, provided, of course, that alkalinity has not accumulated so rapidly that it curtailed molluscan growth early in the history of the lake.

The climatic trends recorded in Fig. 1 for Lake Turkana have some contemporary analogies in Africa. The warm/dry periods which have characterized much of the past at Lake Turkana and which prevail today are also recorded by much the same oxygen isotope ratios in modern gastropods at Lakes Victoria, Edward, Albert and Kivu ($\delta^{18}\text{O}_{\text{PDB}} = 0$ to +4‰), suggesting that temperature more than relative humidity controls the

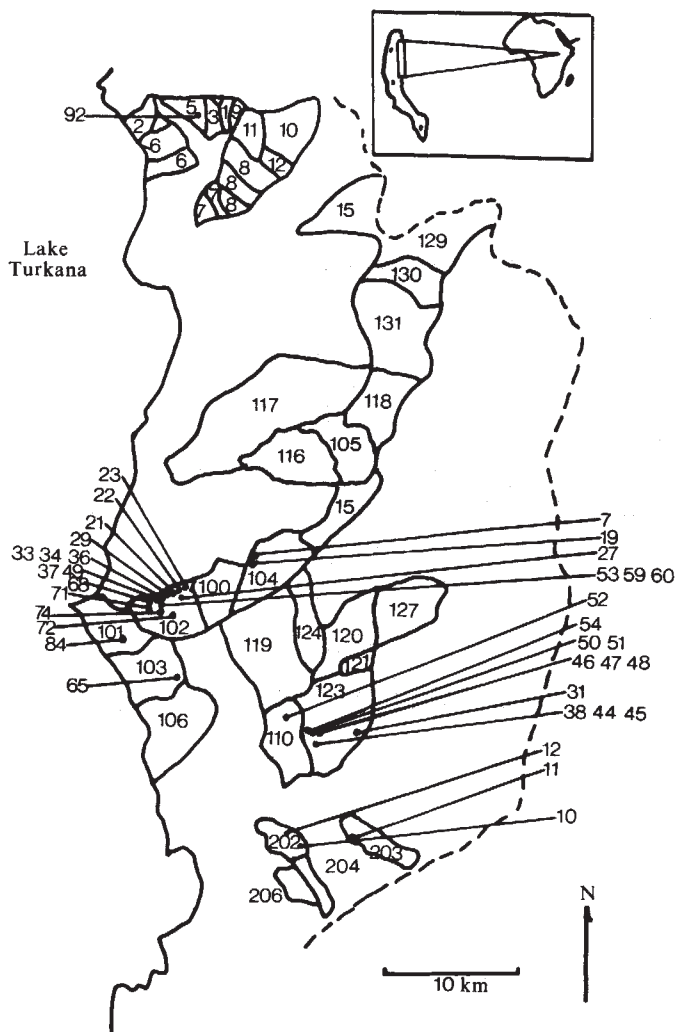


Fig. 2 Koobi Fora region of the Lake Turkana Basin, Kenya, showing the sample numbers (molluscan stratigraphic horizons) and collection sites of the gastropods used in this study in the topographically delineated fossil localities³.

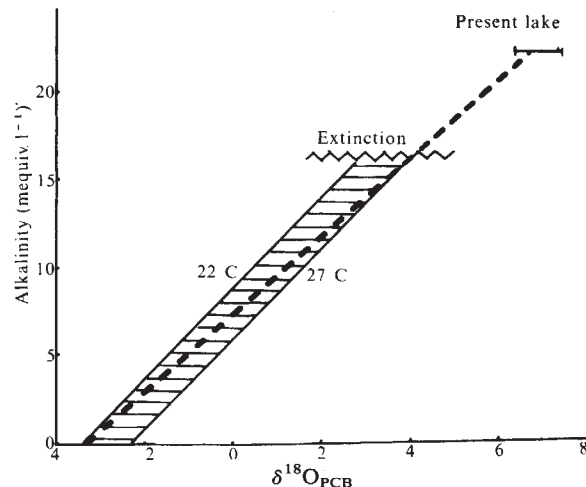


Fig. 3 Change in $\delta^{18}\text{O}_{\text{PDB}}$ of gastropods at Lake Turkana as a function of progressive increase in alkalinity. Meteoric waters, subjected to little evaporative loss, would yield molluscs of $\delta^{18}\text{O}_{\text{PDB}} \approx -4\%$ at near zero alkalinity. Progressive evaporation of the lake in a closed basin would increase the alkalinity and the $\delta^{18}\text{O}$ of the molluscs along the curve to the right. Extinction occurs at an alkalinity of about 16 mequiv. l^{-1} . The cross-hatched area represents temperature effects on $\delta^{18}\text{O}$ (ref. 17), assuming the normal temperature range of contemporary East African lakes of $\sim 5\text{ }^{\circ}\text{C}$ (ref. 18).

evaporative concentration of ^{18}O . On the other hand, the negative values of $\delta^{18}\text{O}$ which have been observed for gastropods of historical times are similar to the isotope ratios of contemporary gastropods of rivers in the Transvaal ($\delta^{18}\text{O}_{\text{PDB}} = -2$ to -4%) or in southern Zaire (-3.5%). Lake Turkana thus had quite a temperate climate at times in the past.

It is unfortunate that the only dated sediments at Lake Turkana are the tuff horizons, so that correlations with the well-dated marine climatic fluctuations cannot be very precise. However, the more important use for this technique is to secure climatic information to be associated with particular fossil beds or archaeological sites, and thus define the climatic component of the evolutionary pressures on the animal population, including man.

I thank Peter Williamson for providing the molluscs for this study, Tom Rockett for assistance in the X-ray analyses, Cecile Vanech for assistance in preparation of the carbon dioxide samples, the Graduate School of Oceanography at this university for use of the mass spectrometer, Andrew Cohen for furnishing samples of contemporary molluscs from Lake Turkana, the Museum of Comparative Zoology of Harvard University for providing mollusc samples from many African lakes, and particularly Richard Leakey for field support at Lake Turkana.

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Reconstruction of spatial information in the human visual system

Göte Nyman & Pentti Laurinen

Department of General Psychology, University of Helsinki,
Ritarikatu 5, 00170 Helsinki 17, Finland

The remarkable capacity of an observer to perceive and recognize objects and forms independent of the exact nature of their components can be described as a process of reconstruction. We have measured the ability of human observers to recognize square-wave or sinusoidal gratings when presented as a pattern of regularly taken spatial samples (see Fig. 1). To recognize the waveforms, the observer must visually reconstruct them from the samples—a process which can be described by the Shannon–Whittaker theorem^{1, 2} of sampling and which Barlow suggests may be carried out by the numerous stellate cells of the visual cortex³. We report here that at low spatial frequencies, relatively more sample lines per spatial cycle were needed for wave recognition than were needed at higher frequencies. However, a square-wave grating was still recognized easily even when it was sampled at a rate at which its third harmonic could not be recognized when presented alone. At high spatial frequencies the square wave was identified when the sampling rate was so low that it caused the third harmonic to be under-sampled. This contradicts the idea that a complex wave is analysed by parallel spatial frequency channels^{4, 5} and emphasizes the capacity of the visual system to use signal features other than the harmonic frequency components of an image to recognize it.

From the Shannon–Whittaker sampling theorem^{1, 2} we know that a signal having a limited bandwidth B can be completely reconstructed from samples provided that the samples are taken densely enough, that is, above the minimum sampling frequency of $2B$ (the Nyquist frequency). The signal can be reconstructed by suitable interpolation between the samples or, conversely, by reconstruction filtering. In the psychophysical context described here, the term 'reconstruct' refers to the observer's ability to perceive certain predetermined spatial features, such as waveform or spatial frequency, in a stimulus consisting of spatial samples of a grating of particular waveform and spatial frequency. The sampling theorem cannot be applied to spatial vision in a straightforward manner, because the number of samples per cycle needed for signal reconstruction actually depends on the spatial frequency value of the grating (that is, the number of cycles deg^{-1} the grating subtends at the observer's eye). When viewed close to, the coarsely sampled gratings on the right and left in Fig. 1 cannot be recognized as sinusoid and square wave, respectively, but at far enough distance the 'grating Gestalts' become visible in the sampled images.

We have measured psychophysically how many samples per spatial cycle are needed to recognize sinusoidal and square-wave gratings. Two gratings were presented successively for 600 ms. The first was always a 'sampled' grating consisting of vertical sample lines of width 4 min. The samples were taken either from a sinusoid with contrast $c = 0.80$ or from a square wave with $c = 0.63$, where $c = (L_{\max} - L_{\min}) / (L_{\max} + L_{\min})$ and $L_{\max}$ and $L_{\min}$ refer to the maximum and minimum luminances, respectively, in the grating. With these contrasts the fundamental frequency component of the square wave and the sinusoid of corresponding spatial frequency both have the same energy content. The samples were taken at regular intervals and presented against a background of constant mean luminance, 120 cd m^{-2} . The second stimulus was a continuous grating, also vertical, but with lower contrast (0.50 in sinusoids and 0.31 in square waves). This made the perceived contrast of the reference and the sampled grating approximately similar. The

subject had to indicate whether or not the appearance of the first grating, the sampled one, matched the reference grating in certain required properties. The density of sampling was increased or decreased according to the response, to determine the subject's threshold. Dense sampling results in a clearly visible grating of continuous appearance, when the sampling rate is decreased, the sample lines become visible, but a total 'grating Gestalt' can still be seen.

Two different threshold criteria were used. First, the subject decided whether he could see the same spatial frequency and waveform in both of the gratings. If he could not, the sampling rate was increased, otherwise it was decreased. Then he indicated when he was sure that no features of the reference grating waveform remained in the sampled image. This was done in order to estimate how much the criterion level shifts affected the results. The thresholds were measured separately for the sinusoids and the square waves and four spatial frequency values were used. The threshold sampling rate was calculated as the mean of the 10 last minimum and maximum values occurring during a threshold run.

The results are expressed in terms of sampling efficiency, which relates the measured threshold sampling rate to the Shannon–Whittaker or Nyquist limit of the grating frequency which was studied. The sampling efficiency $E(s) = N(s)/S(s)$, where s is the spatial frequency, $N(s)$ is the corresponding Nyquist rate and $S(s)$ is the measured value. Thus, $E(s)$ describes the functional sampling efficiency of the visual system in recognition tasks which require spatial interpolation or reconstruction. The results in Fig. 2 indicate that almost identical $E(s)$ values were obtained for the two different waveforms. For both waveforms, $E(s)$ increased as a function of spatial frequency. When the spatial phase of the grating at which the sampling started had the value $0, \pi/4, \pi/2, 3\pi/4$ or π , similar results were obtained, suggesting that the phase was not critical. This was not surprising because the sampling efficiency was rather low at the spatial frequencies used, at 8 c deg^{-1} being still

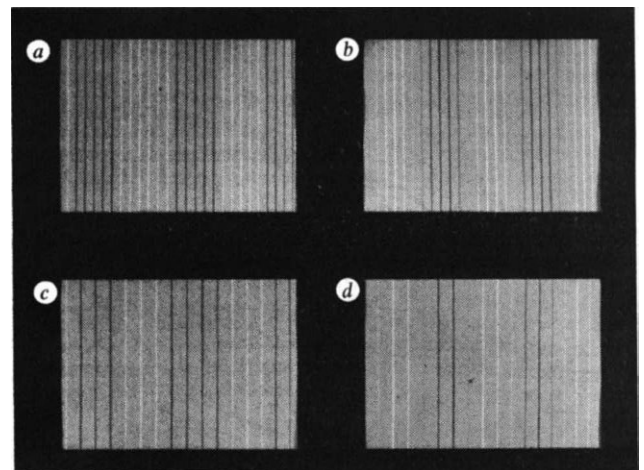


Fig. 1 Spatial sampling effects in grating perception. Square-wave (a, c) and sinusoidal (b, d) gratings of equal spatial frequency have been sampled at regular intervals. Only the sample values carry the grating information and the spaces between them have a constant background value. a, b, Sampling rate of 11 lines per cycle. Increasing the viewing distance (that is, the spatial frequency of the gratings and the angular sampling density) makes it easier to identify the two waveforms even though the physical sampling constraints remain the same. c, d, The same gratings as in a and b, but with sampling density of 7 lines per cycle. The waveforms can be recognized only by increasing the viewing distance sufficiently. The edges of the square wave (a, c) are seen first and it does not have the appearance of its fundamental frequency component. Furthermore, both waveforms are identified simultaneously when the viewing distance is increased. Quantitative results of the sampling and reconstruction effects are presented in Fig. 2.

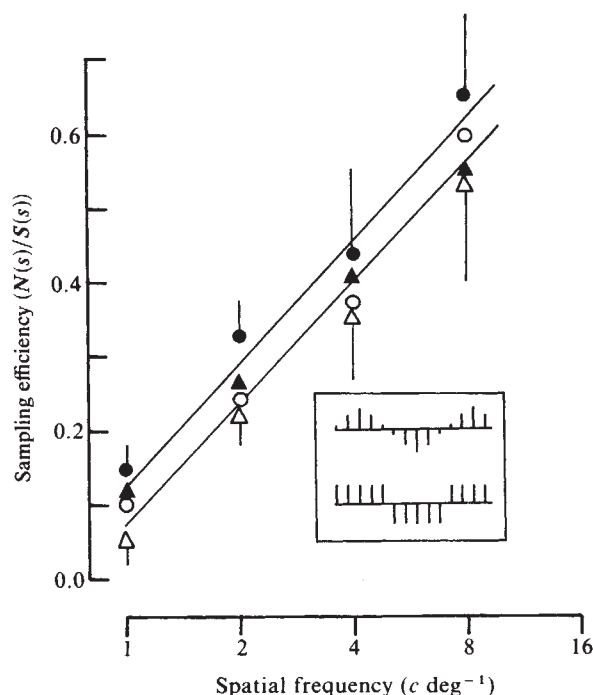


Fig. 2 Sampling efficiency of human spatial vision. We studied the number of sample lines per cycle needed for grating waveform recognition. Two different waveforms were used: ▲, △, sinusoid; ●, ○, square wave. The stimuli from which the samples were taken had contrasts of 0.80 and 0.63, respectively, which makes the energy content of the sinusoid equal to that of the fundamental component in the square wave having the same spatial frequency. The subject adjusted the density of sampling in the grating until he decided that it had the required appearance. Two criteria for the appearance were used: threshold for recognizing the waveform (open symbols) and threshold for the disappearance of the recognizable waveform (filled symbols). The threshold value was taken as the mean of the last 10 settings. The results are expressed in terms of sampling efficiency, $E(s) = N(s)/S(s)$, where $N(s)$ is the Nyquist sampling frequency at spatial frequency s and $S(s)$ is the threshold value obtained. Viewing was monocular, with natural pupil. Mean luminance was 120 cd m^{-2} , the grating size $28 \times 21 \text{ cm}$, and viewing distance 798 cm . Results for one subject (P. L.), an experienced and emmetropic observer, are shown. Experiments with three other subjects gave similar results. The bars represent 1 s.d. and for clarity, only some representative s.d. values are shown. The lines have been drawn by eye and indicate the results for the two different waveforms. The inset describes the waveforms sampled.

~0.6. Changing the threshold criteria caused an average change of 0.10 in efficiency.

If the sampled square wave is recognized when enough of its harmonics contribute to its appearance, then it follows that the sampling rate needed for its recognition should be high enough to make these harmonics recognizable when presented alone. In contrast, the results show that the square wave was recognized even if it was sampled at a rate at which the third harmonic could not be seen. Furthermore, for higher spatial frequencies, the threshold sampling rates for identifying the square wave grating were so low that an efficiency value better than 0.33 was achieved, indicating that the third harmonic of the image must have been undersampled.

Our results contradict the models which describe the visual system as a Fourier analyzer in which a complex waveform is recognized on the basis of the information obtained from its harmonics, each of which is channelled through its own spatial frequency selective channel^{4,5}. The visual system can also use other features than the harmonic frequency components of an image to recognize it. In the case of a high frequency square-wave grating it performs better than expected on the basis of

the sampling theorem. Such performance is known to be possible in some artificial signal processing systems^{6,7} and has also been demonstrated for a model of cortical information processing^{8,9}.

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Local cerebral glucose utilization in non-rapid eye movement sleep

C. Kennedy*†, J. C. Gillin‡, W. Mendelson‡, S. Suda*, M. Miyaoka*, M. Ito*, R. K. Nakamura§, F. I. Storch‡, K. Pettigrew||, M. Mishkin§ & L. Sokoloff*

* Laboratory of Cerebral Metabolism, † Biological and Adult Psychiatry Branches, § Laboratory of Neuropsychology, and || Theoretical Statistics and Mathematics Branch, National Institute of Mental Health, US Public Health Service, Department of Health and Human Services, Bethesda, Maryland 20205, USA
† Department of Pediatrics, Georgetown University School of Medicine, Washington, DC, USA

Sleep is accompanied by alterations in neurophysiological activity in many discrete regions in the brain¹. Such alterations could be expected to be accompanied by corresponding changes in local metabolic rate². We have now looked for the specific regions involved in sleep, at least in the stages other than rapid eye movement (REM) sleep, by using the [²⁻¹⁴C]deoxyglucose method for measuring local cerebral glucose utilization³ in the rhesus monkey. Contrary to what many have predicted, animals during stages 2–4 of sleep exhibited a non-selective, generalized 30% decrease in cerebral metabolic rate. Of the 75 structures measured, none exhibited a higher rate in non-REM sleep than in wakefulness.

The study was carried out in four awake and four sleeping rhesus monkeys weighing 3.8–5.9 kg. They were surgically prepared several weeks before the experiment with electrodes implanted over the dura, in the orbital region and in neck muscles to permit electrical monitoring of cerebral, ocular and muscular activities. The animals spent daytime hours in cages in which they were free to move. To accustom them to the experimental conditions, we placed them in a restraining chair at a regular hour in the early evening. The chair was moved to a ventilated, darkened chamber in which white noise was continuously generated at an intensity of 70 dB to mask adventitious sounds outside the chamber. The animals readily accepted this environment and would sleep normally each night.

On the day of the experiment catheters were inserted in the femoral artery and vein of one leg to allow the intravenous administration of ¹⁴C-deoxyglucose and arterial sampling. This was done under light halothane anaesthesia, from which they took 5–10 min to recover. Three hours later the animals were placed in the sleep chamber. The experimental procedure was initiated in the four sleeping animals ~5 min into the period of slow-wave sleep that immediately followed the first period of REM sleep. Three of the control (awake) animals were also allowed to fall asleep. Five minutes after their first period of REM sleep, however, they were aroused by a gentle jostling of the chamber after which the experiment was begun. The jostling was occasionally repeated when necessary to maintain

wakefulness. A fourth awake control was studied before the onset of sleep. In addition to polygraphic monitoring, a video camera in IR light was used to assess the animal's degree of consciousness during the experiment. In the four sleeping animals, on the average 23 min of the 30 min experimental period was occupied by sleep stages 3 and 4. There were occasional, randomly distributed lapses into stage 2 which lasted on the average 5 min. These lapses took place in only two monkeys during the crucial first 15 min and both lasted 1.5–2 min. Periods of REM sleep and wakefulness, averaging 1 min each, occurred during the last 10 min, when their effect on the results would be negligible due to the relatively low concentration of deoxyglucose in the blood at that time.

The experiments were initiated by an intravenous pulse of 2-deoxy-D-[1-¹⁴C]glucose (specific activity 50–56 mCi mmol⁻¹) dissolved in physiological saline in a dose of 100 µCi per kg. The procedure was carried out as previously described⁴. For each animal, approximately 400 brain sections in the Horsley–Clarke frontal plane were prepared for quantitative autoradiography together with a smaller number for histological staining. The local rates of glucose utilization were calculated from 12 measurements of optical density for each of 75 structures in each animal, by means of a transmission densitometer. The aperture used was 0.5 or 0.25 mm, depending on the size of the structure. When the location of a small nucleus in the autoradiograph was uncertain, positive identification was made with the aid of an adjacent histological section stained with cresyl violet.

Midway through the procedure, arterial blood was sampled for the determination of pH and the partial pressure of the respiratory gases. The mean values $\pm$ s.e.m. of 7.47 ± 0.01 ,

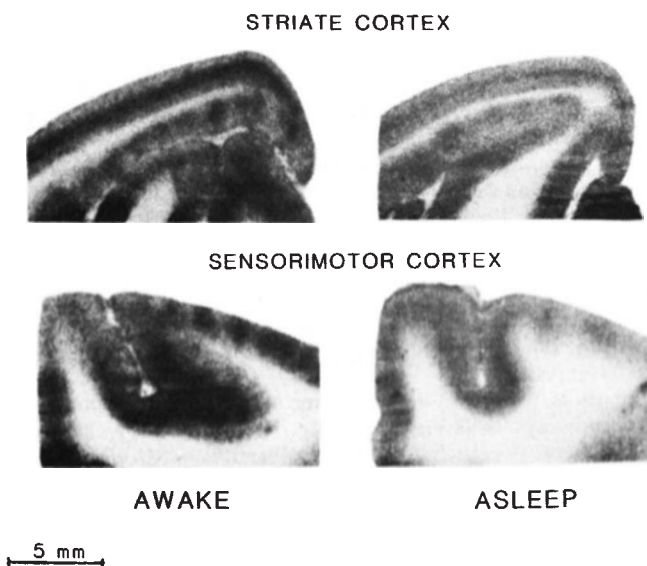


Fig. 1 ¹⁴C-deoxyglucose autoradiographs of coronal sections of striate/prestriate cortex (above) and sensorimotor cortex (below) of monkey brain. The sections on the left are representative of the group of awake monkeys, those on the right, of the group asleep. In the striate/prestriate cortex of the awake monkey, the dark bifid line parallel to the cortical surface corresponds to Layer IV. Fine, regularly spaced markings perpendicular to the cortical surface traverse the entire cortical thickness. Directly beneath the cortex on the upper surface and parallel to it is part of the prestriate cortex. Here Layer IV is not seen but there are rather broad perpendicular markings which are irregularly spaced. In the corresponding section of striate/prestriate cortex of a sleeping animal (upper right), these markings are virtually indistinguishable. The narrow dark and light bands (lower right hand side of the section from the sleeping animal) are artefacts due to wrinkling of the section at the time of cutting. In the sensorimotor cortex of the awake animal (lower left), both perpendicular and horizontal markings are seen. In sleep (right), all these markings virtually disappear in both cortical regions, and the metabolic rate is nearly uniform in the various cortical layers.

Table 1 Glucose utilization in monkey brain during slow-wave sleep (µmol per 100 g per min)

Structure	Awake (n = 4)	Asleep (n = 4)	% Change	P value
Cerebral cortex				
Striate	46 ± 3	30 ± 5	-35	<0.05
Inferior parietal	44 ± 2	28 ± 2	-38	<0.01
Auditory	81 ± 2	46 ± 0.1	-44	<0.0001
Accessory auditory	45 ± 3	36 ± 2	-21	<0.05
Somatosensory	59 ± 8	42 ± 2	-28	<0.1 > 0.05
Motor	44 ± 3	32 ± 2	-26	<0.05
Inferior temporal	48 ± 3	40 ± 3	-16	0.1
Cingulate	51 ± 4	35 ± 4	-30	<0.05
Perirhinal	27 ± 2	22 ± 2	-21	<0.2
Prefrontal	59 ± 6	43 ± 3	-28	<0.05
Medial orbital	51 ± 4	34 ± 1	-17	<0.01
Thalamus				
Lateral geniculate body	43 ± 1	25 ± 1	-41	<0.0001
Medial geniculate body	73 ± 2	46 ± 1	-37	<0.0001
Dorsal medial n.	53 ± 3	34 ± 2	-37	0.001
Ventral post. lat. n.	43 ± 3	30 ± 1	-29	<0.01
Lateral dorsal n.	43 ± 3	27 ± 2	-37	<0.01
Central lateral n.	44 ± 2	30 ± 6	-33	0.05
Midline n.	37 ± 4	28 ± 2	-23	0.10
Anterior n.	39 ± 1	33 ± 4	-17	0.2
Anterior medial n.	52 ± 6	34 ± 2	-33	<0.05
Reticular n.	28 ± 3	17 ± 1	-40	<0.02
Pulvinar	43 ± 1	29 ± 2	-32	<0.001
Ventral anterior n.	39 ± 2	26 ± 2	-34	<0.01
Lateral habenula	48 ± 3	41 ± 3	-14	0.2
Medial habenula	35 ± 2	28 ± 2	-21	<0.05
Hypothalamus				
Ventromedial n.	26 ± 1	21 ± 2	-20	<0.1 > 0.05
Supraoptic n.	29 ± 1	22 ± 2	-23	<0.02
Suprachiasmatic n.	28 ± 2	22 ± 1	-21	<0.05
Medial mamillary n.	63 ± 4	47 ± 1	-26	0.01
Preoptic area	27 ± 1	21 ± 2	-22	<0.05
Lateral hypothalamic n.	26 ± 1	21 ± 2	-18	<0.1 > 0.05
Limbic system				
Lateral amygdaloid n.	31 ± 3	25 ± 2	-20	0.1
Basal amygdaloid n.	27 ± 2	22 ± 1	-16	0.2
Hippocampus	34 ± 3	28 ± 2	-19	<0.1 > 0.05
Hippocampal gyrus	39 ± 3	30 ± 3	-24	<0.1 > 0.05
Dentate gyrus	34 ± 3	28 ± 2	-16	0.2
Lateral septal n.	22 ± 2	20 ± 2	-9	0.5
Medial septal n.	29 ± 2	21 ± 1	-29	<0.01
Substantia innominata	26 ± 2	18 ± 1	-29	<0.01
Extrapyramidal motor system				
Caudate n.	59 ± 5	44 ± 2	-26	<0.05
Putamen	59 ± 4	49 ± 1	-18	<0.05
Globus pallidus	24 ± 2	20 ± 1	-15	0.1
Nucleus accumbens	35 ± 4	29 ± 2	-15	0.3
Clastrum	27 ± 2	24 ± 2	-11	0.4
Subthalamus n.	62 ± 5	40 ± 2	-35	<0.01
Substantia nigra	34 ± 3	24 ± 1	-30	0.02
Red nucleus	49 ± 3	36 ± 1	-27	<0.01
Brain stem and midbrain				
Reticular mesencephalic n.	33 ± 1	21 ± 2	-36	<0.001
Oculomotor n.	59 ± 3	46 ± 2	-23	0.01
Interpeduncular n.	41 ± 2	38 ± 3	-6	0.6
Superior olive	93 ± 14	68 ± 5	-27	0.1
Raphe n., dorsal	34 ± 3	29 ± 2	-16	0.2
Raphe n., ventral	35 ± 4	28 ± 2	-22	0.1
Reticular n., magnocellular	34 ± 3	25 ± 2	-26	<0.05
Locus coeruleus	33 ± 3	27 ± 3	-19	0.2
Superior colliculus	55 ± 2	37 ± 2	-33	<0.001
Inferior colliculus	160 ± 10	126 ± 13	-21	<0.1 > 0.05
Central gray substance	36 ± 1	27 ± 3	-25	<0.02
Ventral tegmental n.	37 ± 2	28 ± 2	-23	<0.05
Vestibular n.	78 ± 8	59 ± 5	-25	<0.1 > 0.05
Cochlear n.	67 ± 1	64 ± 2	-5	0.1
Caud. mesenceph. retic. n.	34 ± 1	24 ± 3	-29	<0.02
Solitary tract, n.	38 ± 5	32 ± 4	-15	0.4
Area postrema	31 ± 0.6	20 ± 2	-36	0.001
Cerebellum				
Crus I	34 ± 2	24 ± 3	-30	<0.05
Vermis	36 ± 2	24 ± 1	-33	<0.01
Flocculus	53 ± 3	28 ± 2	-46	<0.001
Dentate n.	61 ± 6	49 ± 3	-19	0.1
White matter				
Corpus callosum	13 ± 0.7	10 ± 1	-20	<0.05
Anterior commissure	10 ± 0.3	10 ± 0.5	-7	0.3
Internal capsule	14 ± 1	12 ± 0.9	-15	0.3
Corona radiata	8 ± 0.6	5 ± 0.4	-38	<0.01
Optic tract	18 ± 4	14 ± 0.3	-21	0.4
Fasciculus retroflexus	32 ± 1	24 ± 2	-23	<0.02
Pyramids	10 ± 2	7 ± 1	-36	0.1

Values are mean $\pm$ s.e.m.

40 ± 2 , 88 ± 2 mm Hg for pH , P_{CO_2} and P_{O_2} , respectively, in awake animals were not significantly different from those of 7.43 ± 0.02 , 46 ± 2 and 91 ± 3 in sleep.

The rates of local cerebral glucose utilization in the awake controls in this study were similar to those previously obtained by Kennedy *et al.*⁴ in awake animals in the laboratory, except for the rates in a few structures of the auditory and visual pathways. The alterations in these structures could be accounted for by the differing environmental conditions.

In the present study, mean rates of glucose utilization were lower in sleeping monkeys than in awake controls in each of the 75 structures examined, and the difference was significant ($P < 0.05$) in 44 cases (Table 1). The reductions were largest and most consistent in cerebral cortex, cerebellum and thalamus, but no anatomic or functional system was selectively affected, and in no structure was the value in sleep above that during wakefulness. There is, therefore, no evidence to suggest that any cerebral centres were activated during slow-wave sleep. Rates of glucose utilization in the cerebral cortex of the awake animals were seen to be variable in the autoradiographs, which revealed dark markings perpendicular to, and in some areas also parallel to, the cortical surface. Such markings were found in nearly all the major subdivisions of the cortex and, in some cases, the pattern was characteristic for the given area, such as the striate cortex (Fig. 1). This variable pattern of metabolic rates, reflecting the columnar organization of cortical function, virtually disappeared from all regions of the cortex in sleeping animals (Fig. 1).

It has recently been reported that the rate of glucose utilization in the choroid plexus of the cat is elevated in slow-wave sleep⁵. Although the kinetics of deoxyglucose in this tissue has not been sufficiently analysed to ensure accurate quantification of its rate of glucose utilization, the calculation used in this study for brain tissue probably provide at least an index of its metabolic rate. We used a computerized image-processing system⁶ to obtain values for choroid plexus in the monkeys. The brain sections containing this tissue were enlarged 15 times to display the irregular borders which then could be traced with an outline marker. Thus it was possible to obtain an integrated value for the structure in each section. Values did not vary significantly in the lateral, third and fourth ventricles, and no statistically significant differences were found between sleeping and waking animals.

It was possible to calculate a single weighted average rate of glucose utilization of the brain as a whole by scanning all sections with the computerized image-processing system previously described⁶. The mean $\pm$ s.e.m. was 35 ± 2 μ mol per 100 g per min for the four awake control animals. This value was not statistically significantly different from the value of 36 ± 1 μ mol per 100 g per min found by Kennedy *et al.* for the previously published results from seven conscious monkeys studied in the ambient environment of the laboratory⁴. Thus the awake control animals in the present study did not have a generalized activation of cerebral metabolic rate due to the experimental conditions, such as the confinement in a closed chamber and the acoustic stimulation. In the four sleeping monkeys, the average rate of cerebral glucose utilization was 25 ± 1 μ mol per 100 g per min, a statistically significant reduction ($P < 0.02$) below either of the awake groups.

The results of this study might seem inconsistent with those of Mangold *et al.*⁷, who used the Kety-Schmidt method and found no difference in cerebral metabolic rate between slow-wave sleep and wakefulness in human subjects. In five subjects, cerebral oxygen consumption declined during sleep, but in the remaining subject it increased by 34%. As a result, in the group as a whole, cerebral oxygen consumption was not statistically significantly different in sleep and wakefulness. The large difference in the one subject, however, indicates that this subject is a statistical outlier by the criteria of either Grubbs⁸ or Dixon⁹. Thus there is a statistical rationale for his elimination from the series. Mangold *et al.*⁷ had no reason to discard the findings on the basis of the subject's behaviour or any aspect of the pro-

cedure, but had they done so for the statistical reasons cited, the mean value for cerebral oxygen consumption in the remaining five subjects would have declined during sleep by a statistically significant ($P < 0.03$) 11%. The earlier study in man would then be qualitatively consistent with the findings reported in the present studies in the monkey. The discrepancy in the magnitude of the effects may be due to differences in the methods, species, or conditions in which the studies were conducted. In the present study, the measurements were made at the usually normal sleeping time of the monkeys; in the earlier studies in man, the measurements were made at 4:00–6:00 a.m. following deprivation of sleep at the normal scheduled time, and the individuals could have been fatigued.

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Organelle movement in axons depends on ATP

Richard J. Adams

MRC Cell Biophysics Unit, 26–29 Drury Lane,
London WC2B 5RL, UK

When living axons are examined in the light microscope many of the membrane-bounded organelles they contain can be seen to undergo rapid saltatory movements, predominantly in the retrograde direction¹. This is thought to be an important component in the fast transport of materials in axons, the mechanism of which is unknown although cytoskeletal elements such as actin filaments and microtubules are probably involved (see ref. 2 for review and refs). I describe here experiments in which giant axons from the legs of the crab *Carcinus maenas* have been made permeable to ions and small molecules using a high voltage discharge to puncture holes in the plasma membrane³. This allows, in a suitable buffer, movement to be arrested due to the loss of metabolites and then reactivated by the addition of exogenous ATP, thus showing directly for the first time that rapid saltatory motion in axons is an ATP-requiring process.

Electrically active giant axons (~ 30 μ m in diameter) from the walking legs of *C. maenas* were dissected in sea water or in a standard reactivation buffer (400 mM K glutamate, 150 mM glycine, 10 mM EGTA, 20 mM HEPES pH 7.2, 15 mM MgCl₂) at room temperature (about 20 °C). This was carried out in a 5-cm plastic Petri dish in the base of which a 1-cm hole had been drilled and a poly-L-lysine-coated⁴ glass coverslip inserted. The polylysine allows the axons to adhere strongly to the glass coverslip so that high magnification phase contrast objectives may be used. A region of axon with particles exhibiting saltatory movement was selected for permeabilization, and the dielectric breakdown of the plasma membrane was then brought about by the discharge of a 1 μ F capacitor across the axon between two fine stainless steel electrodes held in micromanipulators. A discharge voltage of 70–80 V with the electrodes set 160 μ m apart (about 5 kV cm⁻¹) gave the best results and a series of holes were made in this way at intervals of 10–20 μ m over a distance of 2 mm. The exact size of the holes produced is not known but can be inferred, from the results shown below, to allow molecules of molecular weight at least 900 to pass into and out of the axon; tracer studies

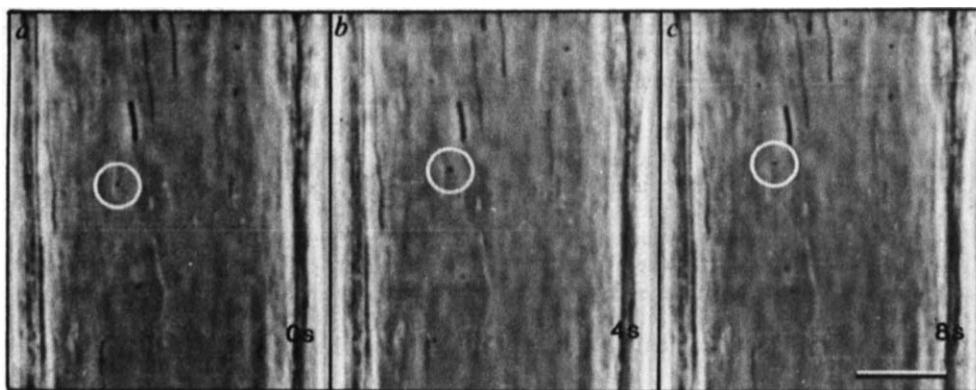
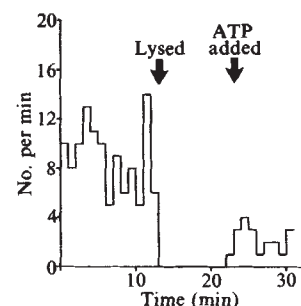


Fig. 1 A sequence of photographs of a particle (encircled) moving in an unlysed axon. The axon was mounted as described in the text and viewed with a Zeiss IM35 inverted microscope. Photographs were taken at the indicated times using Ilford FP4 film. Scale bar, 10 μm .

with adrenal medullary cells³, have shown that this procedure produces holes of about 4 nm diameter. The stability of the holes made in the axon was shown by the observation that the axoplasm of permeabilized but not intact axons was rapidly liquified by the addition of millimolar concentrations of calcium (in the absence of protease inhibitors). It could thus be shown that the holes remain open for at least 2 h; experiments were not continued for longer than this as both permeabilized and intact axons seems to lose their ability to sustain movement after this time *in vitro*.

Movements in axons dissected from the crab leg and mounted in reactivation buffer were similar to those described in other systems^{1,5}. Particles underwent transient movements at rates of up to $2 \mu\text{m s}^{-1}$ with the majority (>80%) travelling in the direction of the cell body (Fig. 1). Many particles that did not undergo persistent movement underwent oscillations of small amplitude (<1 μm) along the axis of the axon. Mitochondria, which in these axons reach up to 50 μm in length, moved only occasionally, but at high rates when they did so. On permeabilization in reactivation buffer lacking ATP, movement progressively declined, with first the large and then the smaller particles coming to rest; the mitochondria often fragmented to give the

Fig. 2 Number of particles passing a cross-section of axoplasm perpendicular to the long axis of the axon. The graph shows particles moving in a single axon before permeabilization ('lysis'), after permeabilization, and after reaction with 6 mM ATP.



appearance of beads on a string. The decline in movement depended on the loss of ATP, ADP and arginine phosphate by diffusion into the external medium. The method given above resulted in a complete cessation within about 5 min of making the holes. The decline could be accelerated, however, by the inclusion of 10 mM 2-deoxyglucose in the medium which greatly increased the rate of ATP (and thus arginine phosphate) turnover; 2-deoxyglucose was not routinely used.

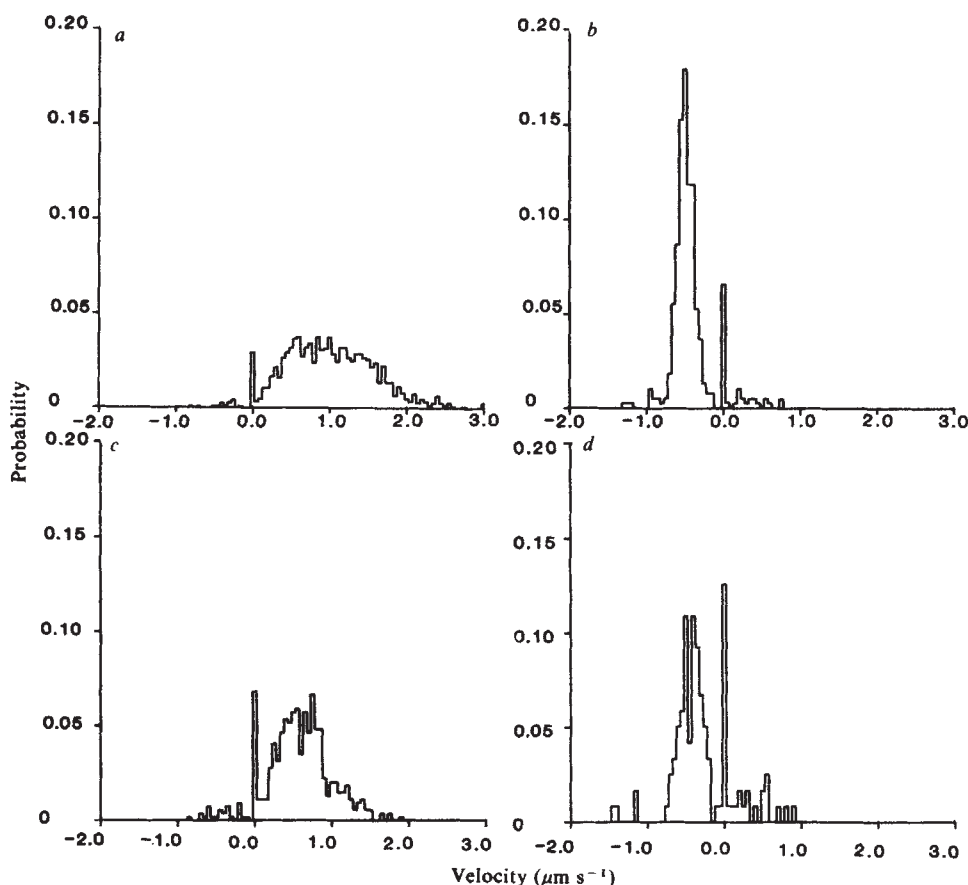


Fig. 3 Instantaneous velocities of particles moving in: *a*, *b*, intact axons; *c*, *d*, axons reactivated in 6 mM ATP. Particles are grouped according to their major direction of transport: *a*, *c*, towards the cell body (retrogradely); *b*, *d*, away from the cell body (anterogradely). Instantaneous velocities were calculated from the time particles took to pass between gradations on an eyepiece graticule corresponding to $0.97 \mu\text{m}$ along the axon. Times were recorded initially on a cassette tape and then analysed by a computer program which calculates the velocity over each increment. The graphs represent the normalized distribution of velocities from several particles in each case: *a*, 1,251 velocity measurements from 18 particles; *b*, 380 from 5 particles; *c*, 542 from 15 particles; *d*, 119 from 5 particles.

Movement was rapidly restored by the addition of ATP; the usual concentration used was 6 mM but as little as 500 μ M could restore some movement. Movement could be reactivated in axons within 90 min following permeabilization; and persisted for up to 2 h in exogenous ATP. The extent of reactivation, as measured by the number of particles passing a point per minute, varied between experiments, ranging over 25–70% (Fig. 2). This variation may be due to both the more erratic nature of movements after reactivation and a reduction in the average velocity at which particles moved. A study of instantaneous velocities (here defined as the velocity over a distance of 1 μ m) of particles moving in unlysed and reactivated axons showed a reduction in the mean velocity of retrogradely moving particles (Fig. 3). The average velocity may have decreased because the conditions of reactivation were less than optimal, although ATP did not seem to have a limiting effect as further increases in its concentration did not increase the rate of movement.

Movement was not reactivated by either GTP (6 μ M) or the non-hydrolysable ATP analogue adenylylimidodiphosphate (AMPPNP, 6 mM). However, the addition of 6 mM ADP did restore some movement. This may have been due to the action of adenylate kinase, a ubiquitous enzyme which can produce ATP from ADP (2 ADP $\rightleftharpoons$ ATP + AMP), as the restoration of movement was prevented by an inhibitor of adenylate kinase (500 μ M P^1 , P^5 -di(adenosine-5')pentaphosphate⁶). This inhibitor (diadenyl pentaphosphate) did not inhibit movement in the presence of exogenous ATP. It appears that the functional integrity of the axoplasm depends on the anion included in the reactivation mixture; movement continued if glutamate was replaced with aspartate but not with α -ketoglutarate, tartrate, methanesulphonate or chloride ions. However, L-glutamate could be replaced by D-glutamate without loss of activity, suggesting that a specific interaction is not involved but that merely stabilization of the structure occurs, as predicted from their relative positions in the lyotropic series. Movement in permeabilized (but not intact) axons was completely inhibited by vanadate ions at a concentration of 500 μ M, although a reduction in the number of particles moving in reactivated axons was seen at concentrations as low as 5 μ M. Vanadate ions in this range prevent mitosis⁷ and ciliary beating⁸ and inhibit the activity of a number of ATPases and kinases⁹.

The buffer in which reactivation was achieved did not contain exogenously added Ca^{2+} and included 10 mM EGTA. An increase in the EGTA concentration to 50 mM had no apparent effect on reactivation. Although it remains possible that a local release of Ca^{2+} occurs from the organelles themselves and is required for them to move, this seems unlikely considering the long duration (up to 2 h) in which movement can continue in EGTA. Inclusion of the calmodulin inhibitor trifluoroperazine to a concentration of 50 μ M does not inhibit movement although at a concentration of 100 μ M movement did appear to decline after ~15 min. It seems unlikely, due to the delay in the effect, that this is a specific inhibition but it may reflect the detergent-like activity of the drug as seen in other systems¹⁰. If Ca^{2+} was added to produce a concentration estimated to be ~1.5 μ M (9 mM $CaCl_2$, 10 mM EGTA, 15 mM $MgCl_2$, pH 7.2) transport still continued for longer than 1 h. The addition of Ca^{2+} at concentrations higher than this is complicated by the presence of Ca^{2+} -activated proteases in the axon which cause its rapid dissolution. However, when the reactivation buffer was supplemented with protease inhibitors (1 mM TLCK, 0.4 μ M acetyl-L-leucyl-L-leucyl-L-arginal, (leupeptin), 0.5 mM phenylmethyl sulphonyl fluoride) movement continued in 0.5 mM Ca^{2+} , in the absence of EGTA, for greater than 1 h. Thus this movement apparently neither requires Ca^{2+} nor is inhibited by high concentrations of Ca^{2+} .

A major aim in the study of cell motility is the establishment of cell-free systems in which movements of interest take place. Only in this way can the components required for movement be analysed and the mechanism of their action determined. The preparation described here is a first controlled step towards a

cell-free system that exhibits fast axonal transport, allowing rapid saltatory movements to occur in axons that have been permeated by a defined mixture of ions and small molecules. The principal conclusion obtained from this system is that the rapid movement of organelles in axons has an absolute requirement for ATP. Furthermore, it seems likely that the hydrolysis of ATP is an essential step in the generation of movement, as it is in the contraction of muscle, the beating of cilia and cytoplasmic streaming in giant algal cells¹¹.

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IgE-dependent release of leukotriene C_4 from alveolar macrophages

John A. Rankin*, Margaret Hitchcock†, William Merrill*, Michael K. Bach‡, John R. Brashler‡ & Philip W. Askenase*

* Department of Medicine, Yale University School of Medicine, PO Box 3333, 333 Cedar Street, New Haven, Connecticut 06510, USA

† Department of Pharmacology, Yale University School of Medicine, The John B. Pierce Foundation, 290 Congress Avenue, New Haven, Connecticut 06510, USA

‡ Hypersensitivity Diseases Research, The Upjohn Company, Kalamazoo, Michigan 49001, USA

Slow reacting substances (SRS) are potent bronchoconstrictors that are thought to be important in the pathophysiology of asthma¹. Human^{2–5} and animal^{6,7} lung fragments release SRS when sensitized by IgE antibody and challenged with specific antigen. SRS have been shown recently to be a family of peptidolipids called leukotrienes (LTC_4 , LTD_4 and LTE_4) that are derived from arachidonic acid^{8–11} and are potent bronchoconstrictors *in vivo* and *in vitro*^{12–14}. It is not known which cell(s) is responsible for releasing SRS but two recent observations have directed our attention to alveolar macrophages. First, Capron and co-workers demonstrated that serum IgE antibody from rats immune to *Schistosoma mansoni* parasites could cause rat peritoneal macrophages to be cytotoxic for schistosomules *in vitro*¹⁵. This is a result of the interaction of IgE with macrophage IgE Fc receptors¹⁶. Similar receptors are also present on rat alveolar macrophages¹⁷. Second, Bach and Brashler^{18–21} established that rat peritoneal macrophages could release a mixture of LTC_4 and LTD_4 when stimulated by the calcium ionophore A23187. We now show that rat alveolar macrophages can be activated by calcium ionophore to release SRS and, when challenged with IgE antibody and specific antigen, release LTC_4 .

Male Sprague-Dawley rats were killed in a CO_2 -filled chamber. Their lungs were lavaged with 150 ml of 0.9% NaCl and the recovered cell suspensions were centrifuged at 500g for 8 min. The cell pellet was washed with 0.9% NaCl, centrifuged and resuspended in Hank's balanced salt solution (HBSS); in mM: $CaCl_2$ 0.95, KCl 5.3, KH_2PO_4 0.4, $MgCl_2$ 149, $MgSO_4$ 0.04, NaCl 136.8, $NaHCO_3$ 4.1, Na_2HPO_4 0.33, glucose 55). The macrophages were identified by uptake of neutral red dye and total cells were counted in a haemocytometer. Viability was assessed by Trypan blue exclusion and the cell number was adjusted to 5×10^6 viable macrophages per ml in HBSS.

Cell differentials on Wright-Giemsa-stained cytocentrifuged preparations revealed the lung lavages to contain 93.2% macrophages, 3.3% lymphocytes, 3.3% neutrophils and 0.14% mast-basophiloid cells (data represent the mean of 15 experiments).

The ability of rat alveolar macrophages to release SRS was tested initially by incubating cell suspensions for 20 min with $1 \mu\text{mol}$ of the calcium ionophore A23187, in the presence of 5×10^{-4} M L-cysteine. In subsequent experiments, cell suspensions were stimulated with purified mouse monoclonal anti-DNP (dinitrophenyl) IgE antibody²² (provided by Dr D. H. Katz) and DNP-human serum albumin (DNP₂₂HSA) in the following manner: cell suspensions were incubated with anti-DNP IgE antibody for 20 min at 37 °C, DNP₂₂HSA was then added and incubation continued for a further 20 min.

Controls consisting of cells alone and cells with antibody alone were incubated simultaneously. Following incubation, the cell suspensions were centrifuged at 500g and the supernatants assayed for SRS on guinea pig ileum in the presence of atropine sulphate ($3.4 \mu\text{g ml}^{-1}$), methysergide maleate ($0.1 \mu\text{g ml}^{-1}$) and mepyramine maleate ($0.34 \mu\text{g ml}^{-1}$). Positive contractions were repeated in the presence of the selective SRS antagonist²³ FPL 55712 ($0.1 \mu\text{g ml}^{-1}$). As the chemical nature of the SRS released by alveolar macrophages was unknown initially, we compared quantitatively the magnitude of the contractions produced by our supernatants with those produced by synthetic (5S, 6R, 7E, 11Z, 14Z)-5-hydroxy-6-[(2R-amino-2-carboxyethyl)thio]7,9,11,14-eicosatetraenoic acid²⁴ (LTE₄; kindly made available by Dr M. Rosenberger, Hoffman-LaRoche). LTE₄ is a constituent of SRS that appears with biologically generated LTC₄ and LTD₄.²⁵ Thus, our data are expressed in $\text{mol} \times 10^{-10}$ of LTE₄ equivalents per 5×10^6 alveolar macrophages.

Figure 1 shows that the non-immunological stimulus A23187 induced the release of SRS ($3 \pm 1.1 \times 10^{-10}$ mol of LTE₄ equivalents). Cells incubated in identical conditions without A23187 and L-cysteine showed no spontaneous release of SRS. Thus, rat alveolar macrophages can release SRS when stimulated by the calcium ionophore.

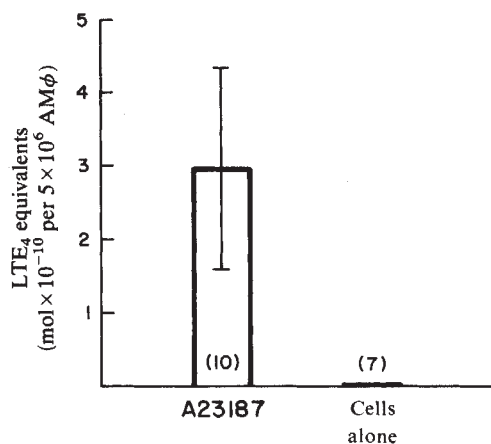


Fig. 1 A23187-induced release of SRS from alveolar macrophages. Rat lung lavages consisting of 93.2% alveolar macrophages and only 0.14% mast-basophiloid cells were adjusted to 5×10^6 viable alveolar macrophages per ml and were incubated at 37 °C with 5×10^{-4} M L-cysteine for 150 s and then for 18 min with $1 \mu\text{M}$ A23187. After centrifugation the supernatants were assayed for SRS on guinea pig ileum in the presence of atropine ($3.4 \mu\text{g ml}^{-1}$), mepyramine ($0.34 \mu\text{g ml}^{-1}$) and methysergide ($0.1 \mu\text{g ml}^{-1}$). Positive contractions were repeated in the presence of $0.1 \mu\text{g ml}^{-1}$ FPL 55712 and were inhibited by 80–100%. Measured contractions were compared with a synthetic LTE₄ standard. LTE₄ equivalents are shown on the ordinate in $\text{mol} \times 10^{-10}$ per 5×10^6 alveolar macrophages. The columns represent mean values for the experiments performed. The number of experiments is shown at the base of the columns; bars represent standard errors.

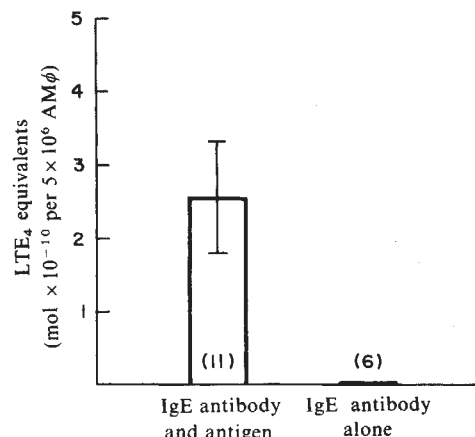


Fig. 2 SRS released from rat alveolar macrophages: induction by mouse monoclonal anti-DNP IgE and DNP₂₂HSA. Cells were prepared and SRS assayed as described in Fig. 1 legend. Positive contractions were inhibited by 100% in the presence of $0.1 \mu\text{g ml}^{-1}$ FPL 55712. LTE₄ equivalents are shown on the ordinate in $\text{mol} \times 10^{-10}$ per 5×10^6 alveolar macrophages. The columns represent the mean values for SRS released, and the bars show the standard error. The number of experiments is shown at base of columns. Alveolar macrophages were incubated with hapten affinity-purified anti-DNP IgE antibody ($10 \mu\text{g}$) for 20 min at 37 °C and for an additional 20 min with DNP₂₂HSA (100 ng). In control experiments, alveolar macrophages were incubated with IgE alone.

Figure 2 shows the pooled results of 11 experiments in which cell suspensions were incubated with anti-DNP IgE for 20 min, followed by a further 20 min incubation with DNP₂₂HSA. Alveolar macrophages also released SRS by this IgE-dependent reaction ($2.5 \pm 0.8 \times 10^{-10}$ mol of LTE₄ equivalents). When cells were incubated with antibody alone (Fig. 2), or with antigen alone, no SRS was released (data not shown). Thus, immunological release of SRS by alveolar macrophages probably depends on a combination of specific IgE antibody and antigen.

Supernatants generated in additional experiments using anti-DNP IgE and DNP₂₂HSA were subjected to chemical analysis in order to characterize the nature of the SRS. Pooled supernatants were deproteinized by 1:4 dilution with methanol and centrifugation, stored at -70 °C, thawed, concentrated, hydrolysed in 0.1 M NaOH, desalted and then chromatographed on a Florisil column with elution in a methanol/water gradient¹⁹. All biological activity eluted in the same position as synthetic LTC₄ standard (prepared by Dr D. R. Morton, Upjohn) and LTC₄ derived from rat peritoneal macrophages^{19,21}. The single peak was concentrated and applied with ³H-labelled LTC₄ tracer (NEN) to a reverse-phase HPLC column ($10 \mu\text{m}$ Nucleosil C-18), eluted isocratically with 65% methanol, 35% water and 0.01% acetic acid, pH 5.4. The absorption at 280 nm, the biological activity and the radioactivity all co-eluted from the column, while a synthetic LTD₄ standard was clearly resolved from the elution peak of the radiolabelled LTC₄ in a separate run on the same column. Thus, two different chromatographic procedures showed that supernatants from alveolar macrophages, activated by an IgE-dependent reaction, contained predominantly LTC₄.

We have thus demonstrated that (1) rat alveolar macrophages release SRS when stimulated non-specifically by the calcium ionophore A23187 in the presence of L-cysteine, and (2) IgE antibody and appropriate antigen cause alveolar macrophages to release SRS leukotriene, LTC₄. Calcium ionophore has been used previously to elicit SRS release from mouse and rat peritoneal mononuclear cells^{18,26}, human leukocytes²⁷, rat basophilic leukaemia cells^{28,29}, and mouse mastocytoma cells³⁰. However, our results differ from previous studies in two ways. First, Orange *et al.*²⁶, using a different strain of rat and a different concentration of L-cysteine, elicited "very little" SRS from alveolar macrophages with A23187. We calculate that the total amount produced by IgE-stimulated alveolar macrophages is

of the same order of magnitude as produced by ionophore-stimulated rat peritoneal macrophages. Second, Bach *et al.*, in collaboration with Capron and Joseph, reported that activation of rat peritoneal macrophages by IgE-anti-IgE—conditions that cause release of lysosomal enzymes³¹—failed to elicit SRS release³². We have, in fact, confirmed this result: when rat peritoneal cells were incubated with anti-DNP IgE and DNP₂₂HSA in conditions identical to those used for our alveolar macrophages, they did not release SRS (data not shown). Thus, alveolar macrophages may be specialized to perform this function. Furthermore, alveolar macrophages release predominantly LTC₄ in an IgE-dependent mechanism whereas rat peritoneal macrophages when stimulated with A23187, release both LTC₄ and LTD₄^{20,21}. In our experiments, it is probable that alveolar macrophages are the source of SRS because alveolar macrophages comprised 93% of the cells in the lung lavage, and when lavage cells were first allowed to adhere to glass for 1 h they were also capable of IgE-dependent release of SRS (data not shown). However, we cannot exclude the possibility that the minority cells present in our cell suspensions (such as mast-basophiloid cells) contributed to the detected SRS either directly³³ or indirectly¹.

The exact mechanism by which IgE antibody and antigen effect SRS release remains to be determined. Capron and co-workers established that complexes of IgE and schistosome antigen were responsible for eliciting cytotoxicity for schistosome larvae in rat peritoneal macrophages³⁴ and Dessaint and co-workers showed that IgE binding to Fc receptors on these cells is of much lower affinity than IgE binding to mast cells¹⁶. Thus IgE antibody and antigen may effect SRS release from alveolar macrophages through formation of immune complexes that activate the cells via these lower-affinity Fc receptors. However, it is also possible that a cytophilic mechanism, analogous to that which sensitizes mast cells and basophils for IgE-dependent release of histamine, is responsible, as 'direct' cytophilic antibodies with high affinity for murine macrophage Fc receptors do exist—but they may be specific for IgG2a³⁵. Our preliminary experiments indicate that both mechanisms may be involved because washing the cells after incubation with IgE and before addition of antigen reduces, but does not eliminate, SRS release. Further experiments are being conducted to investigate this issue further.

The relevance of our findings to allergic lung disease mechanisms remains to be determined. It is clear that many important mediators are released by mast cell-dependent pathways¹ and there is recent evidence that pulmonary mast cells may be an important source of SRS in humans³³. However, it has also been demonstrated recently that human alveolar macrophages can release lysosomal enzymes and superoxide anion after incubation with IgE and anti-IgE antibody, or with serum from allergic patients and the appropriate allergen³⁶. Merrill and co-workers have examined the immunoglobulins present in the lung lining fluid of the lower respiratory tracts of normal individuals, and found that although IgG and IgA were the predominant immunoglobulins present, IgE was present in detectable quantities in ~80% of the 43 people tested³⁷. Similar studies on asthmatic individuals have not been reported, but IgE levels are increased in the nasal secretions of patients with allergic rhinitis³⁸⁻⁴⁰ and probably result from local production⁴¹. As the mucosa of the nose and lower respiratory passages are in many ways similar, it is reasonable to hypothesize that IgE-antigen-macrophage interactions occur on the air-surface interface of the lung. Our demonstration that rat alveolar macrophages release SRS by an IgE-dependent mechanism raises the possibility that IgE-dependent release of mediators by alveolar macrophages may have a role in asthma or other immunologically mediated lung diseases.

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Corticotropin releasing factor produces behavioural activation in rats

Richard E. Sutton, George F. Koob*, Michel Le Moal*, Jean Rivier & Wylie Vale

Peptide Biology Laboratory and * Arthur Vining Davis Center for Behavioral Neurobiology, The Salk Institute, PO Box 85800, San Diego, California 92138, USA

A 41-residue peptide with high potency and intrinsic activity to stimulate the secretion of corticotropin and β -endorphin by the adenohypophysis has been characterized and synthesized^{1,2,19}. From experience with other hypophysiotropic and brain peptides³⁻⁵, and studies suggesting that CRF could act centrally to activate the sympathetic nervous system (M. Brown *et al.*, in preparation), we considered it likely that this corticotropin/ β -endorphin releasing factor (CRF) would have direct behavioural actions. We decided to investigate the effects of CRF on a simple measure of activation in the rat, locomotor activity in photocell cages. We report here that centrally injected synthetic CRF produces a dose-dependent locomotor activation in rats. This increase in activity was not produced by peripheral administration of CRF. In an open field test, rats receiving centrally injected CRF exhibited behaviour consistent with an increase in emotionality. These results suggest that CRF may have an activating action in the central nervous system independent of its effects on the anterior pituitary gland.

Table 1 Effects of CRF (i.c.v.) on behaviour of rats in open field

	Crossings* inner	Crossings outer	Rearing* free	Rearing wall	Rearing duration (s)	Grooming duration
Saline	7.9±3.0	96.4±7.6	4.9±1.4	33.3±3.7	44.0±4.7	29.4±6.6
CRF (0.0015 nmol)	14.6±4.6†	90.1±10.4	9.4±3.3	34.9±3.7	42.1±4.1	38.1±14.2
CRF (0.015 nmol)	5.1±1.3	92.3±13.4	2.3±0.6	24.4±3.6	37.8±8.1	30.6±8.9
CRF (0.15 nmol)	1.9±0.6	29.1±7.5‡	0.0±0.0‡	4.3±1.5‡	7.1±2.3‡	90.9±18.4‡

* $F_{\max}$ $P < 0.05$: raw data square root transformed for ANOVA; *a posteriori* tests were only made after obtaining significant differences using ANOVA. † Significantly different from CRF 0.15 nmol group, Newman-Keuls test $P < 0.05$. ‡ Significantly different from saline group, Newman-Keuls test $P < 0.05$.

In the initial experiments the subjects were male albino Wistar rats (200–230 g at the time of injection) which were group housed and maintained in a temperature- and light-controlled environment. For the intracerebroventricular (i.c.v.) injections, rats were equipped with a cannula aimed above the lateral ventricle. For this surgery, the animals were anaesthetized with Chloropent (Fort Dodge Laboratories) and secured in a Kopf stereotaxic instrument with guinea pig ear bars. A 7-mm long, 23-gauge stainless steel guide cannula was lowered within 1 mm of the ventricle and anchored in place with two stainless steel screws and dental cement. With the tooth bar 5 mm above interaural zero, coordinates were -0.6 mm posterior to bregma, ± 2.0 mm lateral and -3.2 mm below the skull surface at the point of entry. For an injection, the dummy stylet was removed and an 8-mm 30-gauge stainless steel cannula with 1 m of Tygon microbore tubing (Norton Plastics and Synthetics) was inserted through the guide.

CRF, synthesized by the solid phase method on a paramethylbenzylhydrazide resin using previously described techniques⁶, was purified by HPLC after cleavage and deprotection by HF. The isolated material was shown to be highly purified ($>98\%$) when tested by homogeneity in several reverse phase HPLC systems including analysis of a tryptic digest. As reported earlier, such closely related analogues of CRF as des-Ala⁴¹-CRF, [Met(O²¹)]-CRF, des-Ileu⁴⁰, Ala⁴¹-CRF and CRF-OH could be separated in the chromatographic conditions developed in our laboratory (ref.1 and J.R. *et al.*, in preparation). One hour before injections, the peptide was dissolved in 0.9% saline and kept on ice; 2 μ l of peptide were injected by gravity over a 30-s period simply by raising the tubing above the head of the rat until flow began. Volume was measured by marks on the PEID tubing previously calibrated with a 10- μ l Hamilton syringe. Only those rats whose cannulae flowed easily with this technique were used in the experiment. The lateral ventricle cannula placements were verified by injecting 2 μ l of

toluidine blue dye into the ventricle and immediately killing the rat by decapitation. Of 35 rats tested in this way, all showed spread of the dye throughout the ventricular system. For subcutaneous CRF injections, each rat received the peptide dissolved in 1 ml per kg body weight saline in the neck.

Locomotor activity was measured in a 4×4 bank of 16 wire cages 20×25×36 cm each with two horizontal IR photocell beams across the long axis 2 cm above the floor. Noncumulative photocell beam interruptions were recorded every 10 min from electromechanical counters located in an adjacent room. Each rat was habituated first overnight and then for 2 h 1 day before peptide injections. On a test day, rats were habituated for 90 min just before peptide injections, which were given at 10 a.m. Results were analysed with a two-factor analysis of variance (ANOVA), with peptide or saline groups being the independent factor and time the repeated measure. If ANOVA revealed a significant ($P < 0.05$) group effect, comparisons of individual means were made using the Newman-Keuls *a posteriori* test.

Open field testing took place in a large open field⁷ measuring 115×115×46 cm tall and divided by thin white lines into 23×23 cm squares. In the open field, the light intensity was ~ 150 ft-candles and the white noise level was 70 dB. The open field was enclosed by sheets of one-way viewing sunscreen. Naive rats were tested in a 5-min session by placing the rat in the centre of the open field. The following behavioural measures were taken by two blind observers: rearing—inner and outer squares; locomotion—inner and outer squares, time rearing, time grooming and number of grooming bouts. Here, the rats were injected with 0.0015, 0.015 and 0.15 nmol of CRF 1 h before testing.

CRF injected i.c.v. produced a dose-dependent increase in activity as measured by photocell interruptions (Fig. 1). This increase in activity was significant at the 0.15 and 1.5 nmol doses. Rats injected with saline habituated rapidly, showing low photocell counts after 1 h, but rats given 1.5 nmol CRF had high counts for over 5 h post-injection (data not shown). Repeated i.c.v. injections of CRF over several days did not modify this increase in behavioural activity. Following injections, rats in the photocell cages were observed through a one-way mirror. In addition to normal locomotion and sniffing, the rats injected with 0.15 and 1.5 nmol CRF exhibited a unique set of behaviours which seemed to reflect a general behavioural activation. These included elevated walking, grooming and rearing. The elevated walking was characterized by rhythmically walking forwards and backwards such that only the toes of the rat touched the cage. The rats frequently climbed up and down the two mesh sides of the photocell cages, and they also engaged in other repetitive locomotion such as moving forwards and backwards in a straight line with their head along the ground and sniffing vigorously. While rearing, rats pawed rapidly against the sides of the cages. When returned to their home cages, the rats exhibited an increase in mounting behaviour and aggressivity.

Although other peptides, such as endorphins and ACTH, have been shown to produce increases in behavioural activity^{8–11}, the time course and nature of the response observed with CRF differed dramatically from the responses observed with endorphins. Opioid peptide activation following i.c.v. injection consists of an initial depressant phase which varies in duration with the dose and of a staring behaviour that

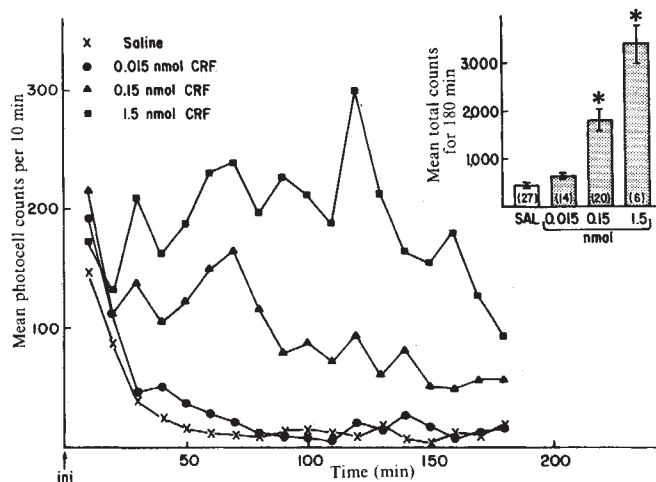


Fig. 1 Locomotor response after i.c.v. infusions of 0.1, 1 and 10 μ g corresponding to 0.015, 0.15 and 1.5 nmol of CRF, respectively. Ordinate refers to total photocell counts for each 10-min period of a 3-h test. * Significantly different from saline, and from each other. $P < 0.05$, Newman-Keuls test following analysis of variance. Mean total counts for 180 min represent average $\pm$ s.e.m.

approaches a catatonic-like state at higher doses. CRF did not produce these responses, nor the bursts of locomotor activity interrupted by scratching and grooming behaviour observed with opioid peptides⁸, nor the well-documented 'stretching-yawning syndrome' (SYS) observed after i.c.v. injection of ACTH and ACTH-like peptides⁹⁻¹². In contrast, the activation produced by CRF at the lower doses appeared to be an exaggeration of normal activation produced by introduction into a familiar environment. At the highest dose, the behaviour was characterized by the more bizarre elevated walking and rhythmic walking forwards and backwards.

Results in the open field test indicate that rats receiving CRF i.c.v. in a novel environment respond in such a way as to be consistent with an increased emotionality or increased sensitivity to the stressful aspects of the situation. Here, the rats at the 0.15 nmol dose of CRF showed decreases in locomotion and rearing, but increases in freezing behaviour. These behavioural responses are characteristic of an increase in emotional reactivity (Table 1). Typically, a rat injected with 0.15 nmol CRF and placed 1 h later in the open field moved hesitantly to the outer squares of the open field. The animal then either slowly circled the open field, remaining close to the floor and wall with virtually no rearing, or remained in one of the corners grooming or moving forwards and backwards. In contrast, control animals injected with saline rapidly circled the open field initially with a substantial amount of rearing and later in the 5-min period made forays into the inner squares with some free rearing. Interestingly, at the lowest dose of CRF, 0.0015 nmol, there were some increases in rearing and locomotion (Table 1) that would be considered more consistent with the activation observed in the photocell cages described above.

Subcutaneous injections of identical doses of CRF failed to produce significant effects in the open field test, although the highest dose produced some trends in the same direction. These trends were not statistically significant by ANOVA, nor are these results of similar magnitude to those observed by central injections. For example, the largest effect of the peripheral injection was a 46% decrease in wall rearings in the open field at the 0.15 nmol per rat dose compared with an 87% decrease following central injection (ANOVA $P > 0.10$). Also, there was a complete blockade of the free rearing with the 0.15 nmol dose injected i.c.v. but only a 37%, not statistically significant, change following the same dose injected subcutaneously. Thus, these preliminary results suggest a relatively minor contribution of the systemic actions of the peptide for the open field effects. In addition, subcutaneous injections of 0.015, 0.15, 1.5 and 7.5 nmol of CRF failed to increase locomotor activity significantly in the photocell cages (data not shown). These results together suggest that CRF is acting centrally to produce its behavioural activation, as these systemic doses are capable of producing significant elevations of plasma ACTH and β -endorphin.

Although these results suggest that CRF can act centrally to produce a dose-dependent behavioural activation, physiologically CRF might act in concert with ACTH, β -endorphin or glucocorticoids to bring about some behavioural responses to circumstances such as stress. CRF, however, is structurally specific in its behavioural effects, as the C-terminal free carboxyl analogue, which is inactive *in vitro*¹, did not augment locomotor activity to the extent observed with CRF itself. Based on maximal response, this analogue was $\frac{1}{1,000}$ th as potent as CRF in increasing locomotor activity. Sauvagine, a non-mammalian polypeptide with striking homology with CRF¹³ and similar *in vitro* activity²⁰, was equipotent in increasing locomotor activity.

Thus, in a familiar environment (photocell cages) CRF produces a behavioural activation as reflected by a prolonged increase in locomotor activity where similarly treated, saline-injected animals rapidly habituate and go to sleep. However, in a novel stressful environment (open field test), similar doses produce decreases in behaviour such as rearing and inner square crossings that are consistent with an increase in the stress of the situation. How these effects described above extend to other less

stressful situations involving such theoretical constructs as learning and attention remains to be determined.

The present results thus provide evidence that CRF may have neurotropic action independent of the hypophyseal system. These observations, in conjunction with the well documented involvement of β -endorphin and corticotropin in stress¹⁴⁻¹⁸, suggest a possible role of central CRF in similar adaptive mechanisms.

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Dimeric tetrapeptide enkephalins display extraordinary selectivity for the δ opiate receptor

Yasuyuki Shimohigashi, Tommaso Costa, Hao-Chia Chen & David Rodbard

Endocrinology and Reproduction Research Branch, National Institute of Child Health and Human Development, National Institutes of Health, Clinical Center Room 10B17, Bethesda, Maryland 20205, USA

The μ and δ opiate receptors, postulated on the basis of pharmacological observations, have been well characterized in ligand-binding studies¹⁻⁶. The several classes of opiate receptor appear to subserve different functions⁷⁻⁹. Although highly specific μ ligands are available, there has been a paucity of high-affinity ligands with δ specificity that could be used to investigate the functions, properties and spatial distribution of the δ receptor. Previous structure-activity studies of the enkephalins have suggested that a free carboxyl group at the C-terminus is an important determinant of δ selectivity^{9,10}; amidation of Leu⁵ or Met⁵ results in a non-selective ligand. Recently, however, we have demonstrated that cross-linking enkephalin amides by a methylene bridge of suitable length produces a dimeric pentapeptide, with greater affinity and selectivity for the δ receptor than is found in the original δ ligand^{11,12}. Evidence that this dimer may interact simultaneously with two δ , but not two μ receptors¹² is consistent with independent demonstrations that the δ receptors are clustered in the membrane^{7,13}. When the C-terminal amino acid of enkephalin is removed, the resulting tetrapeptide enkephalin amide H-Tyr-D-Ala-Gly-Phe-NH₂ and its analogues are potent and selective

ligands for μ opiate sites^{14,15}. If the δ receptors were closely clustered, as suggested by our findings with dimeric enkephalin pentapeptides^{11,12} and by others^{7,13}, then it might be possible to form a dimeric analogue of the tetrapeptide enkephalin which could interact with two δ receptors but not with two μ receptors. Theoretically, this would confer δ selectivity on the dimer of a μ -selective ligand. We have thus synthesized a series of dimeric analogues of the μ -selective tetrapeptide [D-Ala², des-Leu⁵]enkephalin amide by cross-linking at the C-terminus with NH₂-(CH₂)_n-NH₂, with $n = 2-12$. We report here that the dimer with $n = 12$ has a nearly 1,000-fold increase in δ/μ selectivity ratio, and is thus a δ -selective ligand.

A series of dimeric tetrapeptide enkephalins have been synthesized by a two-step coupling procedure: cross-linking of Boc-Phe-OH with NH₂-(CH₂)_n-NH₂ (where $n = 2-12$), followed by elongation with Boc-Tyr-D-Ala-Gly-OH. Purity was confirmed by mass spectrometry, amino acid analysis and TLC. [D-Ala², D-Leu⁵]enkephalin (DADLE), [D-Ser², Leu⁵]enkephalyl-Thr (DSLET) and monomeric tetrapeptide [D-Ala², des-Leu⁵]enkephalin amide (DAPEA) were purchased from Peninsula Laboratories (San Carlos, California). All peptides were evaluated for their activity in two different radioligand assay systems, using either ³H-DADLE (40 Ci mmol⁻¹; 0.10 nM) and membranes from neuroblastoma-glioma hybrid (NG108-15) cells^{5,16}, or ³H-naloxone (³H-NAL, 50.2 Ci mmol⁻¹; 0.15 nM) in rat brain membrane preparations¹⁷.

In the ' δ receptor' assay, the removal of the C-terminal amino acid residue from the pentapeptides [D-Ala², Leu⁵]enkephalin amide (DALEA) and DADLE, giving the tetrapeptide [D-Ala², des-Leu⁵]enkephalin amide (DAPEA), caused a substantial loss of δ activity (Table 1). When ³H-DADLE was used as the labelled ligand in the assay, DAPEA was approximately 30-fold less potent than DALEA and DADLE. In contrast, the dimeric tetrapeptide enkephalins (DTE_n) were very active for the δ

receptors with IC₅₀ values of 1-4 nM. In particular, DTE₁₀ and DTE₁₂ (with cross-linking methylene chains of $n = 10$ and 12 respectively) were 30-fold more potent than the DAPEA monomer, and were as active as DADLE and DALEA, and more active than [D-Ser², Leu⁵]enkephalyl-Thr (DSLET).

In the ' μ receptor' assay, when ³H-NAL was used as labelled ligand, DAPEA monomer retained high affinity, was only three-fold less potent than DALEA, and was twice as potent as DADLE and 10-fold more potent than DSLET. Dimers with $n = 2-8$ (DTE₂-DTE₈) showed higher potencies than the monomer DAPEA, and had IC₅₀ values of 1.8-2.7 nM. DTE₁₀ was slightly less active than DAPEA. Surprisingly, the dimer of tetrapeptide enkephalins with $n = 12$ (DTE₁₂) showed an extremely low affinity for μ receptors: approximately 28-, 12- and 80-fold lower affinity than DAPEA, DADLE and DALEA respectively.

We may define the δ/μ selectivity ratio (SR) as the ratio of the IC₅₀ using ³H-NAL and whole brain divided by the IC₅₀ obtained using ³H-DADLE and NG108-15 cells (Table 1). A completely non-selective compound with the same potency in both assays should have a ratio of unity⁹. For example, DALEA shows a SR of 0.97, and thus serves as a non-selective ligand. The tetrapeptide DAPEA shows a SR of 0.1, corresponding to its 10-fold preference for μ receptors, while DADLE (SR = 7.2) and DSLET (SR = 20) are δ -selective peptides. Dimers DTE₂ and DTE₄ are non-selective (SR ~ 1), while DTE₆ and DTE₈ slightly favour the μ and δ receptor sites respectively. The dimer DTE₁₀, with a longer cross-linking methylene chain, favours δ receptors (SR = 4.7). The dimeric tetrapeptide enkephalin DTE₁₂ shows an extraordinary selectivity for δ receptors: its SR of 91 is approximately 13 times that of DADLE and 4.5 times that of DSLET, which has been regarded as the most δ -selective ligand available to date. The DTE₁₂ dimer shows a 30-fold greater affinity for the δ receptor and a 30-fold weaker affinity for the μ receptor, relative to the monomer DAPEA.

The inter-relationships among the various ligands are illustrated in Fig. 1. The abscissa indicates the equilibrium constant of association (affinity constant K_μ) estimated using the μ -specific radioligand assay. The ordinate shows the affinity (K_δ) in the δ -specific radioligand assay. The line of identity corresponds to a δ/μ non-selective ligand. The region below the line of identity corresponds to a μ -selective ligand, that above the line to δ -selectivity. Lines corresponding to 10-fold changes in SR are shown. DADLE (point number 1) is the progenitor of the δ -specific ligand, with a K_δ of ~10⁹ but a K_μ of 10⁸. Amidation of [D-Ala², Leu⁵]enkephalin, forming DALEA (point 2), results in loss of selectivity. The amide of the tetrapeptide (DAPEA, point 3) shows ~10-fold selectivity for the μ receptor, consistent with previous reports^{14,15}. However, the dimer of this tetrapeptide with a methylene bridge of $n = 12$ (DTE₁₂, point 4) shows a dramatic increase in δ selectivity ($K_\delta = 10^9$, $K_\mu = 10^7$). Its affinity and selectivity surpass those of DSLET (point 5).

The present results for DADLE and DSLET are consistent with those derived from *in vitro* muscle bioassays. Gacel *et al.*¹⁸ reported that DSLET was seven times more selective than DADLE when evaluated in terms of its inhibitory potencies on the electrically stimulated mouse vas deferens and guinea pig ileum (corresponding to δ and μ bioassays respectively).

The present findings (Table 1, Fig. 1) are consistent with the hypothesis that the dimers of the tetrapeptide can serve as bivalent ligands, binding simultaneously to two distinct but closely clustered δ receptors, but failing to bridge two μ receptors, and complement those for the dimers of the pentapeptide leucine enkephalins, (H-Tyr-D-Ala-Gly-Phe-Leu-NH-)(-CH₂)_n. If the C-terminal leucine residue were approximately as long as a methylene chain with $n = 3$, then chain lengths of $n = 2-6$ for the dimeric pentapeptides would correspond to $n = 8-12$ for the dimeric tetrapeptides. Thus it is not surprising that the most selective and potent tetrapeptide has the longest methylene bridge, whereas the most potent pentapeptide has

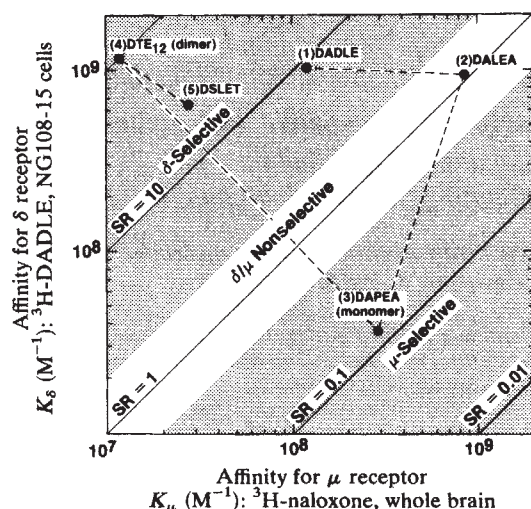


Fig. 1 Two-dimensional display of affinities of enkephalin peptides in a μ -specific radioligand assay (K_μ , abscissa), and in the δ -specific radioligand assay (K_δ , ordinate). Non-selective ligands would fall in the region along the main diagonal, μ -selective ligands below and to the right, and δ -selective ligands above and to the left. Compare (1) DADLE, the δ prototype; (2) DALEA, the amidated pentapeptide enkephalin; (3) DAPEA, the amide of the tetrapeptide [D-Ala², des-Leu⁵]enkephalin; (4) DTE₁₂, the dimer of DAPEA, connected by a methylene bridge with $n = 12$; and (5) DSLET, the best δ -selective ligand previously reported. Fine diagonal lines correspond to 10-fold changes in the δ/μ SR. All affinities were calculated using the formula: $K_1/K_2 = (IC_{50})_2/(IC_{50})_1$, which is valid in the present experimental conditions with low per cent binding of labelled ligand¹⁹. The calculations used the following data, obtained in similar conditions: in the δ activity assay, DADLE shows $K = 1.03 \times 10^9$ M⁻¹ ($N = 4$ expts) and an $IC_{50} = 1.15 \pm 0.07$ nM ($N = 4$); in the μ assay, naloxone displays $K = 6.6 \pm 1.8 \times 10^8$ M⁻¹ ($N = 6$) and $IC_{50} = 1.56 \pm 0.15$ nM ($N = 3$).

Table 1 Receptor binding activities of enkephalin analogues

Enkephalins	IC ₅₀ (nM)		
	δ Activity (³ H-DADLE)	μ Activity (³ H-NAL)	δ/μ Selectivity ratio (IC ₅₀) μ /(IC ₅₀) δ
Monomer			
DAPEA: H-Tyr-D-Ala-Gly-Phe-NH ₂	33.2	3.48	0.10
DALEA: H-Tyr-D-Ala-Gly-Phe-Leu-NH ₂	1.24	1.20	0.97
DADLE: H-Tyr-D-Ala-Gly-Phe-D-Leu-OH	1.15	8.22	7.2
DSLET: H-Tyr-D-Ser-Gly-Phe-Leu-Thr-OH	1.85	37.9	20
Dimers; DTE_n			
DTE ₂	1.68	1.81	1.1
DTE ₄	2.87	2.79	0.97
DTE ₆	3.67	2.28	0.62
DTE ₈	1.46	2.66	1.8
DTE ₁₀	1.04	4.84	4.7
DTE ₁₂	1.06	96.3	91

Results are expressed as the IC₅₀ for each compound in an assay for δ activity using ³H-DADLE (0.10 nM) and NG108-15 cell membranes according to Chang *et al.*^{5,16}, and in an assay for μ activity using ³H-naloxone (0.15 nM) and membranes prepared from whole brain¹⁷. Specific binding was measured as the difference between total binding and that in the presence of 10⁻⁵ M DADLE or 10⁻⁵ M naloxone. Competition curves were analysed by computerized non-linear least-squares estimation of the logistic curves, to obtain an estimate of the IC₅₀ with its standard error²⁰. IC₅₀ values showed a within-experiment coefficient of variation (c.v.) of 6%, and a between-experiment c.v. of 14% for the δ activity assay, with values of 14 and 16% respectively in the μ activity assay. The δ/μ selectivity ratio is defined as the IC₅₀ in the μ assay divided by the IC₅₀ in the δ assay.

the shortest methylene bridge ($n = 2$): the observations for both series of dimers are consistent with very close spacing of δ receptors.

To establish that the special properties of the dimer is due to its bivalency, we are currently synthesizing alkylamidated derivatives of the enkephalin monomers and 'handicapped dimers' with mono-*N*-acetylation of one of the tyrosines in both the tetra- and pentapeptide series. Studies of these new compounds should help to exclude alternative hypotheses to the cross-linking mechanism. Presumably, the lack of increased affinity of DTE_n or DPE_n for the μ receptor is due to a different spatial pattern of μ receptors in the membrane. This rationale has provided a basis for the design and synthesis of what appear to be superior probes of the δ receptor. A similar strategy should be useful in designing ligands with improved affinity and selectivity for a wide variety of other receptor systems for drugs, hormones and neurotransmitters.

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Characterization of the structural gene and putative 5'-regulatory sequences for human proopiomelanocortin

Madeleine Cochet*, Annie C. Y. Chang & Stanley N. Cohen

Departments of Genetics and Medicine, Stanford University School of Medicine, Stanford, California 94305, USA

It is now well established that the hormones corticotropin (ACTH) and β -lipotropin (β -LPH) are contained within a common precursor peptide called proopiomelanocortin (POMC), which is synthesized in the anterior and/or intermediate lobes of the pituitary¹⁻³ and in the hypothalamus⁴. The recent cloning of a 'full-size' cDNA copy of bovine POMC mRNA has revealed the presence of additional peptides in the previously 'cryptic' segment of the precursor protein⁵. This cDNA has been used as a hybridization probe for the isolation and characterization of a bovine genomic DNA segment encoding the complete POMC mRNA⁶, and for isolation of part of the corresponding human genomic DNA sequence⁷. DNA sequence analysis of these isolates and of part of the rat POMC gene⁸ has shown that, in the species studied, certain segments of the POMC structural gene have been conserved during evolution, whereas the nucleotide sequences of other segments have diverged sharply. We have now isolated and characterized a 11.6-kilobase (kb) human genomic DNA fragment that encodes the complete POMC mRNA and putative regulatory sequences proximate to the gene (which is repressed by glucocorticoids *in vivo*⁹). We have also analysed the 800-base pair (bp) segment preceding the mRNA coding sequence, within which—at a position nearly 480 bp upstream from the mRNA start site—is a 21-bp segment that shares homology with a DNA sequence beginning 370 bp upstream from two other glucocorticoid-controlled genes. We speculate that these sequences may be involved in the regulation of POMC gene expression by glucocorticoids.

* Present address: Unité de Biologie Moléculaire du Gène, Institut Pasteur, 28, Rue du Docteur Roux, Paris 75724, France.

Using probes made by nick-translation of segments of a previously characterized human POMC genomic DNA fragment (Fig. 1, probes *a* and *b*)^{7,10}, we screened a human fetal DNA library (a gift of T. Maniatis) by *in situ* hybridization in standard conditions (Fig. 1 legend). Two bacteriophage λ plaques that reacted with probe *a* also hybridized with probe *b*, which only contains sequences corresponding to the 5' end

of bovine POMC mRNA. Analysis of the DNA from these clones by restriction endonuclease digestion and electrophoresis on agarose gels indicated that both included *Eco*RI fragments 11.6 and 4.7 kb long.

DNA from one of these clones (H-POMC λ 5A) was analysed further by electrophoresis of products resulting from single or double digestion with restriction endonucleases (Fig. 1B). Only the E2-E3 segment of the 11.6-kb fragment hybridized to both probes; DNA fragments B3-E3 and P6-E3 hybridized only to probe *a*, which includes all of the protein-coding sequences for ACTH and β -LPH, whereas DNA fragments B2-B3 and P5-P6 hybridized only to probe *b*. These findings suggested that at least a proportion of the sequences encoding the amino-terminal end of the precursor peptide⁵ is contained in fragment B2-B3, and permitted the endonuclease cleavage sites of the genomic DNA fragment to be oriented with respect to transcription (see Fig. 1).

Finer mapping of the B2-B3 fragment following subcloning using the vector pBR322 indicated that sequences homologous to probe *b* are localized to the region surrounding the P5 site (data not shown). The DNA sequence for this region (Fig. 2) was determined according to the strategy shown in Fig. 1B. A high degree of homology was observed for 152 bp (nucleotides +88 to +239) in the region designated as exon 2 in Fig. 2, which is contiguous with a previously identified region of interspecies conservation that begins near the 5' end of exon 3. The conserved region is delineated by intron-exon junction consensus sequences¹¹, which include G-T at the 5' end and A-G at the 3' end of the intron. Exon 2 contains the AUG translational start codon for the POMC peptide, the conserved downstream codons specifying the hydrophobic leader sequences of human and bovine POMC, and only a short (20 bp) segment of the untranslated region of POMC mRNA. Thus, the remainder of the untranslated region was either not present on the 11.6-kb fragment, or alternatively, the lack of detectable hybridization of probe *b* with any other segment of this fragment might be explained by evolutionary divergence in the sequences of the two mammalian genes.

As human POMC mRNA was not readily available, we re-probed the 11.6-kb fragment with the 5' end of bovine DNA, using less stringent hybridization conditions that might allow identification of regions of incomplete homology. Fragments of H-POMC λ 5A DNA generated by *Eco*RI and *Bam*HI endonucleases were subcloned, transferred to aminothiophenol paper (B. Seed, personal communication) after electrophoresis in gels, and hybridized at various temperatures between 45 and 65°C with probe *c*, which contains 107 bp of the extreme 5' end of bovine POMC cDNA (15 bp of which are included in exon 2). At 56°C, the temperature that gave the best signal over background, a positive signal was obtained only with the genomic DNA fragment containing exon 2 (Fig. 3, lane 3) and with the E2-B1 fragment (lane 2). More detailed analysis of fragment E2-B1 (Fig. 3b) localized the homologous sequence to a 160-bp *Ava*I endonuclease-generated fragment near the *Bam*HI terminus of the E2-B1 fragment (Fig. 3b, lanes 3, 4). The DNA sequence of this fragment and the surrounding regions between the *Rsa*I and *Bam*HI sites was determined according to the strategy shown in Fig. 1B.

Alignment of the nucleotide sequence (Fig. 2) with the published sequence for bovine POMC genomic DNA⁶ (starting at position -181) allows assignment of a putative start site for the human mRNA (+1). The dinucleotide G-T is found 87 bp downstream from this start site at the end of a region that contains three segments showing >80% homology with the corresponding bovine sequences (positions +9 to +28, +43 to +63 and +71 to +87). We conclude therefore that this region may contain the first mRNA-coding segment (that is, exon 1) of the human gene, despite its different length from the corresponding bovine segment (87 instead of 108 bp). A 'TATA' box characteristic of an RNA polymerase II (or B) promoter site¹² and a 'CAAT' box¹³ are found 28 and 63 bp respectively upstream from the putative start site of the POMC mRNA at

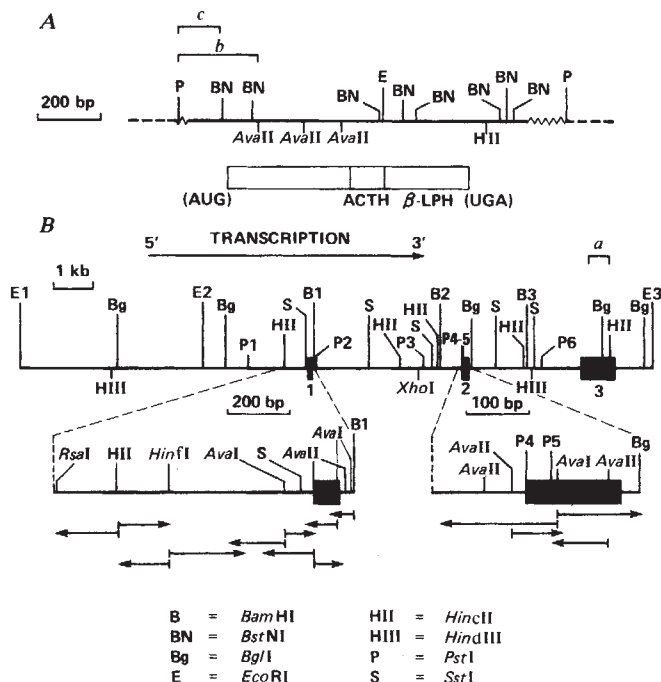
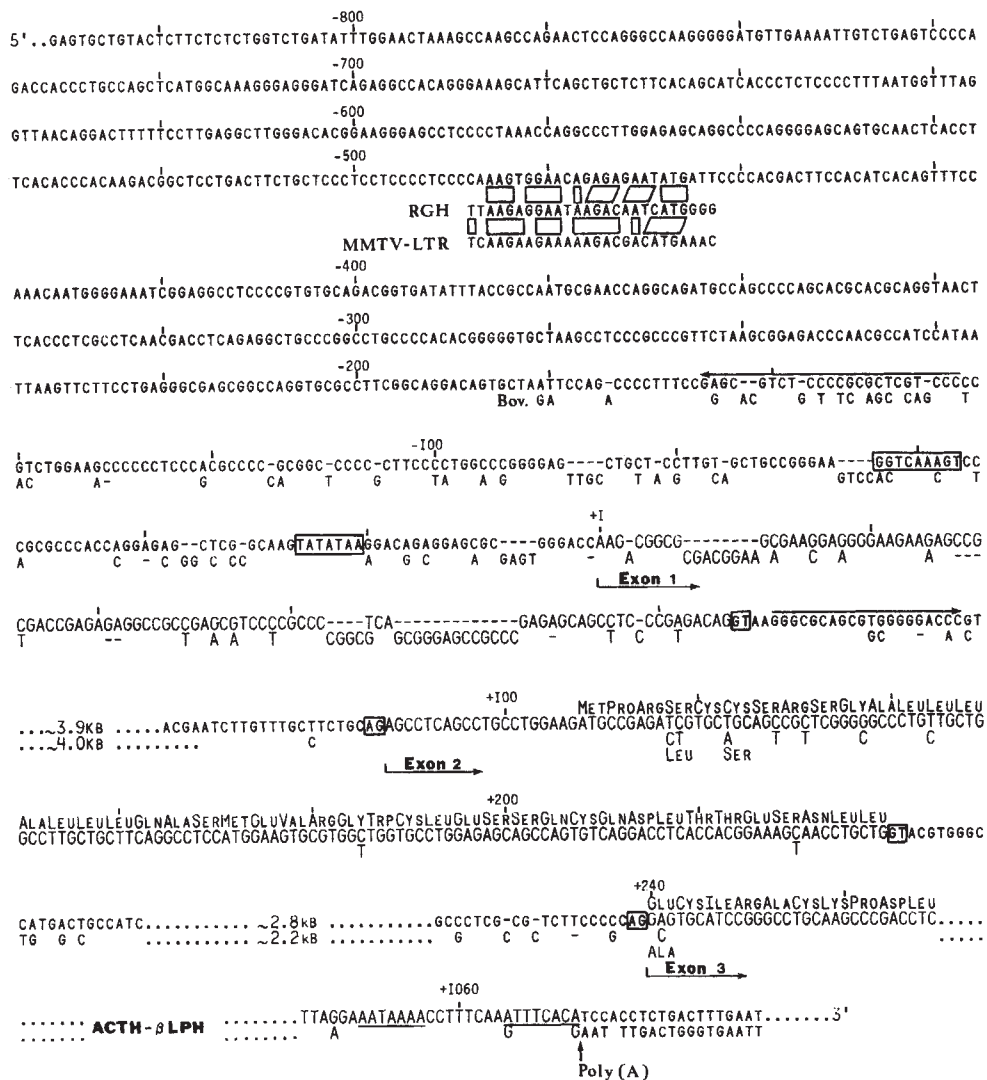


Fig. 1 A, partial restriction endonuclease map of the bovine POMC cDNA insert of pSNAC20 (ref. 5). The broken lines represent pBR322 DNA sequences. The serrated lines represent the 27- and 112-nucleotide poly(dG)-poly(dC) tracts lying at junctions between the plasmid vector and the cloned cDNA. The 5' and 3' termini of double-stranded cDNA are designated according to the corresponding ends of bovine POMC mRNA. *b* and *c* indicate the probes used for the hybridization studies described in the text and were prepared as follows. An *Ava*II endonuclease-generated fragment of the pSNAC20 plasmid, containing 248 bp of the 5' end from the bovine cDNA insert plus 119 bp of pBR322 sequences, was inserted into the *Hinc*II cleavage site of pACYC177 by blunt end ligation after filling-in of the ends by DNA polymerase. The resulting plasmid (pACYC654) was digested by the *Pst*I restriction endonuclease, generating two fragments, one of which contains the 5' end of the bovine cDNA. This fragment (530 bp) was then purified by sucrose gradient centrifugation, and used as probe *b*. Probe *b* was also digested by *Bst*NI endonuclease, giving three fragments, and the resulting 134-bp fragment (which contained most of the sequences corresponding to the 5'-untranslated region of bovine POMC mRNA) was purified by electrophoresis, yielding the *c* probe. The open bar below the POMC cDNA corresponds to the POMC peptide; the initiation and termination codons are in brackets. B, partial mapping of the structural gene encoding human POMC mRNA and strategy of sequencing. The human fetal DNA library used was constructed by inserting DNA fragments from a partial *Eco*RI endonuclease digest into a bacteriophage λ charon 4A vector³⁰. It was screened by *in situ* hybridization³¹ using the nick-translated^{7,10} *a* probe. This probe corresponds to an *Ava*I-*Hinc*II fragment of a human genomic DNA segment previously cloned in the pACYC401 plasmid⁷ and contains sequences encoding the ACTH- β LPH region of POMC. The partial restriction enzyme cleavage map corresponding to the genomic DNA contained in H-POMC λ 5A (one of the two identical clones we obtained) was deduced by analysis of DNA samples singly or doubly digested with restriction endonucleases. The black thick bars and the numbers below them designate DNA sequences corresponding to POMC mRNA (exons). Their positions were determined by hybridization, with the nick-translated probes *a*, *b* or *c*, of endonuclease-treated DNA digests transferred onto nitrocellulose filters³² or aminothiophenol paper (see Fig. 3 legend). Hybridization conditions with probes *a* and *b* have been described previously⁷; conditions used with probe *c* are described in Fig. 3 legend. For convenience, DNA fragments were identified by the abbreviated names of the endonuclease cleavage sites that bracket them, followed by a number designation according to the direction of transcription (for example, E2-E3 is the DNA fragment terminated at the 5' end by *Eco*RI cleavage site number 2 and at the 3' end by *Eco*RI site number 3). The DNA fragments carrying exons 1 and 2 are enlarged in the diagram and the strategy of sequencing is shown. The arrows designate the segments sequenced; the tails indicate the sites of ³²P end-labelling of the fragments.

Fig. 2 Nucleotide sequence of the human POMC genomic DNA strand corresponding to POMC mRNA. Digests of DNA fragments E2-B1 and B2-B3, which had been subcloned using the pBR322 plasmid vector, were digested with *Ava*I, *Ava*II, *Bam*HI or *Hin*FI endonucleases and treated with polynucleotide kinase³³. The nucleotide sequence was then determined³³ by following the strategy of Fig. 1B. The sequence of the strand that corresponds to mRNA is shown. Differences in nucleotides and amino acids in the bovine versus human sequences are indicated below the human DNA sequence. Broken lines represent nucleotides absent from the genomic DNA sequence. Position +1 indicates the putative start site of human POMC mRNA based on known bovine sequences⁶. Nucleotides are numbered plus for exonic sequences downstream from the mRNA start site and minus for sequences upstream from the mRNA start site. The TATA and CAAT sequences, and the A-G, G-T dinucleotides at the intron-exon junctions are boxed. The proposed consensus sequence¹³ for the poly(A) addition site is underlined. The region of dyad symmetry is overlined by arrows. The region of homology between human DNA sequences and RGH²² or MMTV-LTR²³ are shown by boxes; in both RGH and MMTV-LTR, the homologous sequence begins 392 nucleotides upstream from the mRNA start site. Errors in the partial sequence of exon 3 published previously⁷ have been corrected as a result of additional analysis, and the sequence of Chretien^{28,29}. Despite careful



positions similar to those described for other mammalian genes¹⁴. Upstream from the CAAT box of the human POMC gene are runs of nucleotides (positions -64 to -75, -101 to -145, -165 to -179) that are significantly homologous with sequences found in the corresponding positions of the bovine gene; at other locations the bovine and human sequences are highly divergent. Interestingly, a region of very stable dyad symmetry ($\Delta G = -47$ kcal) is located 100 bp upstream from the CAAT box and at the 3' end of intron A, therefore enclosing the CAAT and TATA boxes and all of exon 1.

If the identifications made above on the basis of DNA sequence analysis are correct, the E2-B1 segment of the 11.6-kb DNA fragment cloned in H-POMC λ 5A should contain a promoter for RNA polymerase II. We demonstrated the presence of such a promoter in this region by *in vitro* transcription experiments¹⁵⁻¹⁷ using endonuclease-generated digests of cloned POMC human genomic DNA (plasmids pAP2 and pLEB7) as templates for RNA polymerase II. The plasmids used for these studies contained respectively the human genomic DNA fragments P1-P2 and E2-B1; if the regions identified as TATA and CAAT boxes in these clones are in fact signals allowing initiation of transcription of the POMC gene, digests of pAP2 DNA by *Bam*HI, *Pvu*I, or *Pvu*II endonuclease should yield *in vitro* RNA 'run off'¹⁵ transcripts of 130, 300, and 427 nucleotides respectively, and a digest of pLEB7 DNA by the *Sal*I endonuclease should give a 405-nucleotide

RNA transcript. The RNA transcripts synthesized *in vitro* on cloned POMC genomic DNA have the lengths predicted (Fig. 4). Thus, the sequences we have identified as the putative transcriptional regulatory region for the POMC gene seem capable of directing RNA polymerase II-dependent initiation of transcription *in vitro*.

Much work has focused on the role in gene regulation of sequences immediately upstream from the mRNA-coding regions of prokaryotic¹⁸ and eukaryotic¹⁴ genes, but little attention has been given to the possible influence of more distant upstream sequences. Recently, however, a putative binding sequence for the progesterone-receptor complex involved in the control of egg-white protein synthesis in the chicken oviduct has been identified 250–300 bp upstream from the mRNA start site of the ovalbumin gene¹⁹. In the case of the POMC gene, sequences at an equal or greater distance from the mRNA start site might be important in the glucocorticoid regulation of gene expression, or in the abnormal production of the POMC-derived peptides by certain non-pituitary tumours^{20,21}. To explore the role of more-distant upstream regions in normal and abnormal POMC gene expression, we have determined the primary sequence of the 800-nucleotide segment preceding the POMC mRNA start site.

Comparison of the DNA sequence obtained by such analysis with published sequences of other glucocorticoid-controlled genes showed that between position -486 and -466 upstream

from the POMC mRNA start site is a 21-bp DNA segment (see Fig. 2) that shows 80% homology with a 21-bp stretch beginning 370 bp upstream from the mRNA start site of the rat growth hormone (RGH) gene²². A similar sequence (75% homology) starts at the same location relative to the mRNA start site of the long terminal repeat (LTR) of the mouse mammary tumour virus (MMTV) DNA²³. The expression of both the RGH gene and the MMTV genetic sequence are positively regulated by glucocorticoids^{24,25}, whereas the expression of the POMC gene is negatively regulated by this hormone⁹.

The existence of specific DNA sequences that may be involved in the binding of the hormone-receptor complexes has been suggested recently by *in vitro* studies for the MMTV LTR gene²⁶ and the egg-white protein genes in the chicken oviduct¹⁹. The presence of largely homologous sequences in two gene segments positively controlled by glucocorticoids, and also in

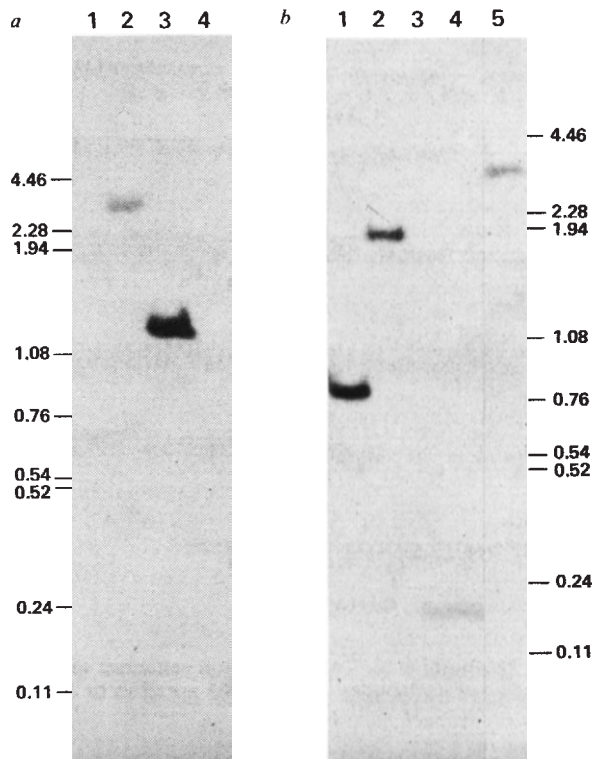


Fig. 3 Detection of the 5'-untranslated region of human POMC mRNA. Genomic DNA fragments E1-E2, E2-B1, B1-B2 and B2-B3 generated by *Eco*RI and *Bam*HI restriction endonuclease digestion of H-POMC λ 5A DNA were subcloned using the pBR322 vector. The DNA of plasmids containing the various fragments was digested by restriction endonucleases, subjected to electrophoresis on 2% agarose gels, transferred on aminothiophenol paper (B. Seed, personal communication) and hybridized to 20 ng of the nick-translated probe *c* (10^8 c.p.m. μ g⁻¹) for 48 h at 56°C in 5×SSC, 0.1 M NaPO₄ pH 6.8, 10× Denhardt's solution³⁴. After hybridization, the filters were washed at room temperature for 10 min in 2×SSC, 0.1% SDS twice, then 10 min in 0.5×SSC, 0.1% SDS once, and subjected to autoradiography for 12 h at -70°C with XR-5 film and Dupont Cronex lightening plus intensifying screen. *a*: Lane 1, 0.4 μ g of E1-E2 fragment digested with *Hind*III endonuclease; lane 2, 0.4 μ g of E2-B1 fragment; lane 3, 0.5 μ g of B2-B3 fragment digested by *Sst*I; lane 4, 0.5 μ g of B1-B2 fragment. *b*, Digests of 0.5 μ g E2-B1 fragment with *Hinc*II endonuclease (lane 1), *Pst*I (lane 2), *Ava*I (lane 3), *Ava*I plus *Pst*I (lane 4). Lane 5 contains undigested DNA. The numbers at the side of the figure indicate the molecular size (in kb) of marker DNA derived from λ wild-type DNA digested by *Hind*III, and SV40 DNA digested by *Hin*I endonuclease. The hybridization signal seen with probe *c* (*a*, lane 3) is more intense than expected. We attribute this effect to slight contamination of probe *c* with probe *b* sequences, despite electrophoretic purification of the *c* probe fragment before use.

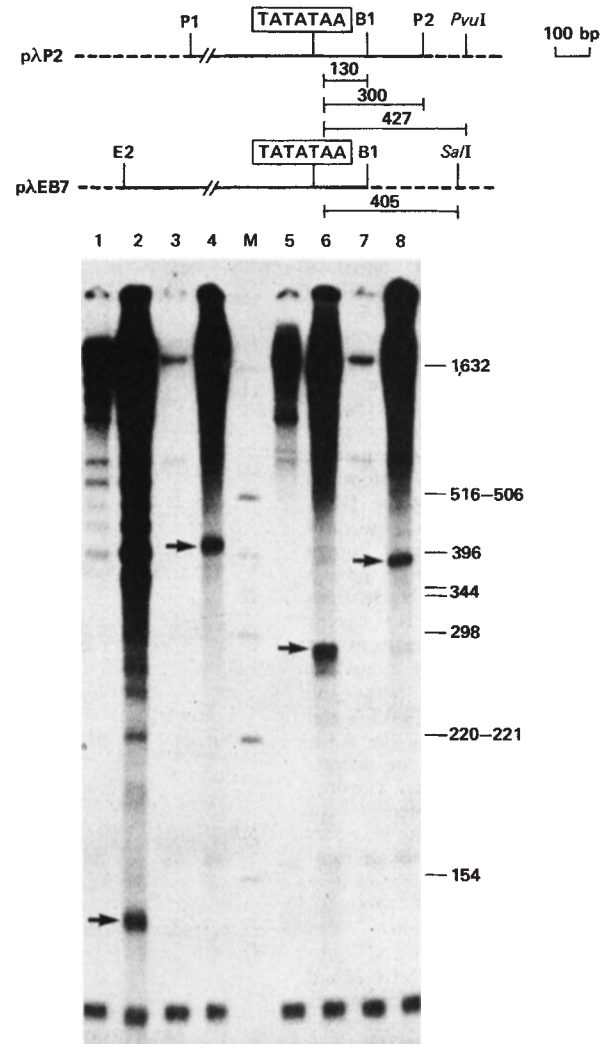


Fig. 4 Run-off analysis of RNA synthesized *in vitro* on human genomic DNA by RNA polymerase II (or B). The DNA fragments E2-B1 and P1-P2 of clone H-POMC λ 5A were inserted into the pBR322 vector, yielding the chimaeric plasmids pλEB7 and pλP2. The resulting DNAs were used as templates for *in vitro* transcription by cell-free extracts of HeLa cells (BRL) as described¹⁷. The DNA fragments were either excised and purified by sucrose gradient centrifugation (fragment P1-P2, lanes 5, 6) or treated with restriction endonuclease and phenol-extracted (lanes 1-4, 7, 8). To differentiate transcripts made by RNA polymerase II (or B) from those resulting from RNA polymerase III (or C), 1 μ g ml⁻¹ of α -amanitin was added to appropriate reaction mixtures (lanes 1, 3, 5, 7). RNA transcripts of the human genomic DNA were purified as described previously¹⁶ and analysed on a 4.5% acrylamide/7 M urea gel. After drying, the gel was exposed to film for 6 h as described in Fig. 3 legend. The length of the RNA transcripts was determined relative to molecular length markers (lane M) consisting of fragments of pBR322 DNA produced by digestion with *Hin*II and ³²P end-labelled. The lengths (in numbers of nucleotides, nt) are labelled on the right side of the panel. The region of initiation of transcription was inferred from the length of the RNA chains which are terminated prematurely by endonuclease digestion of the template DNA at specific sites, and which therefore 'run-off' the template¹⁵. The arrows point to the RNA transcripts described. Lanes 1-4, run-off transcripts of 4.5 μ g of pλP2 double-digested with *Pst*I and *Bam*HI (lanes 1, 2) or *Pvu*I alone (lanes 3, 4). The α -amanitin-sensitive transcript has an apparent length of 135 (lane 2) and 415 (lane 4) nt. Lanes 5, 6, run-off transcripts of 2.8 μ g of the excised P1-P2 fragment. The α -amanitin transcript has an apparent length of 292 nt (lane 6). The molecular weight was calculated for the upper transcript. The smear below is probably due to degradation because it does not appear each time. Lanes 7, 8, run-off transcript of 4 μ g of pλEB7 digested by *Sa*I. The DNA transcript has an apparent length of 390 nt (lane 8).

the region upstream from the negatively controlled human POMC gene, could be accounted for if such sequences are involved in the binding to DNA of the glucocorticoid-receptor complexes. Although the homology in the DNA segments we have identified is incomplete, the occurrence of similar sequences at the same distance upstream from the mRNA start site in RGH and the MMTV LTR is of interest, although their functional significance remains unknown. In any case, the specific DNA sequence we have identified does not seem to be necessary for dexamethasone stimulation of MMTV LTR-regulated gene expression in transfected cells: stimulation still occurs after removal of all MMTV LTR sequences beyond the 170–200 nucleotides immediately upstream from the mRNA cap site (J. Majors and H. Varmus, and G. Ringold, personal communications).

Our data indicate that the 11.6-kb *EcoRI* endonuclease-generated gene fragment E2–E3 includes the entire structural gene for human POMC. The gene's mRNA coding sequences are contained in three exons of 87, 152 and 833 bp, separated by two introns of about 3.9 and 2.8 kb. While segments of both interspecies conservation and divergence exist in the mRNA-coding and non-coding regions of the human, bovine and rat POMC genes, the mRNA of all three species is spliced at identical sites. The longest segments of interspecies conservation occur in the protein-coding region of the gene, especially in the segment that includes the hormones ACTH and β -LPH. However, significant sequence conservation occurs also in the 3'-non-coding region and in a segment upstream from the TATA and CAAT boxes (–64 to –178), suggesting that these regions may be important in the expression of POMC *in vivo*.

After completing this work, we received a manuscript reporting a similar overall structure and DNA sequence of the mRNA-encoding region of the POMC gene and the immediately proximate upstream region²⁷. The protein sequence recently reported in refs 28 and 29 corresponds to the DNA sequence that both we and Takahashi *et al.* have obtained.

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G inversion in bacteriophage Mu: a novel way of gene splicing

Micheline Giphart-Gassler, Ronald H. A. Plasterk & Pieter van de Putte

Laboratory of Molecular Genetics, Leiden State University, Wassenaarseweg 64, 2333 AL Leiden, The Netherlands

The G region of bacteriophage Mu is a 3,000-base pair (bp) invertible DNA segment that determines the host specificity of the phage^{1,2}. Only phage with the G segment in the orientation designated (+) can adsorb to *Escherichia coli* K-12 (refs 3–5), whereas phage with the G segment in the (–) orientation infects other hosts such as *Citrobacter freundii* and *E. coli* C (ref. 1). It has been proposed that four genes are involved in host specificity—*S*, *U*, *S'* and *U'*—of which *S* and *U* are expressed in the orientation (+) and *S'* and *U'* in the inverted orientation (–) of the G segment. We have presented two alternatives for the organization of these genes (Fig. 1). In model A the four genes involved are entirely contained within the G segment, whereas in the alternative model (B) it is assumed that the proximal part of the *S* gene is located in the α part of the Mu genome. We report here that the *S* and *S'* genes are partially located outside the G segment and share a common part located in α (Sc). This common S region will be joined by G inversion to one of the two variable parts (Sv or Sv') which results in the synthesis of either tail fibre protein S or S'.

In both models A and B two predictions were made concerning the *S'* gene: (1) that the structural polypeptide with a molecular weight (Mr) of 48,000 (48K) (see Fig. 2a), which is a component of G(–) phage is indeed the product of a gene located at least partially in G and (2) that this *S'* gene is located in the region of G which is non-essential for G(+) phage⁶. Three Mu amber mutants were isolated which were amber phage on G(–) hosts but wild type on the G(+) host *E. coli* K-12. These amber mutations mapped in the G segment in that part which

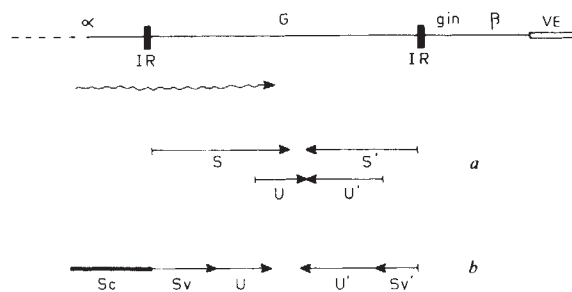


Fig. 1 Two proposed models for the organization of the G region of bacteriophage Mu. The G segment (3 kb) is situated between the α part (~30 kb) and the β part (1.5 kb). The G segment (drawn in orientation +) can invert by recombination between inverted repeats (IR). Amber mutations in genes *S* and *U* have been mapped in G with *U* mutations mapping distal to the *S* mutations¹² and these genes should be located in the leftmost 1,700 bp of G DNA⁶. *S* and *U* are essential for G(+) but not for G(–) phage¹. The *S* protein (56K) and a 21K protein (*U*?) are structural components of G(+) phage particles but not of G(–) phage particles^{1,13}. G(–) phage particles contain two structural proteins of 48K and 26K, tentatively designated *S'* and *U'*, respectively, which do not occur in G(+) phage particles. It is assumed that *S'* and *U'* are involved in adsorption of G(–) phages and that their genes are located in the rightmost 1,300 bp of G DNA non-essential for G(+) phages. To obtain expression of *S'* and *U'* in the G(–) orientation, transcription of G genes starts in the α part of the Mu genome. The four proteins *S*, *U*, *S'* and *U'* require a coding capacity over 4 kb of DNA, a length exceeding the 3 kb G segment. If the four genes are located entirely in the G segment they should overlap (model A). In model B the *S* and *S'* genes span the α -G boundary with a common region in the α segment (Sc) and two variable regions at the ends of the G segment (Sv and Sv').

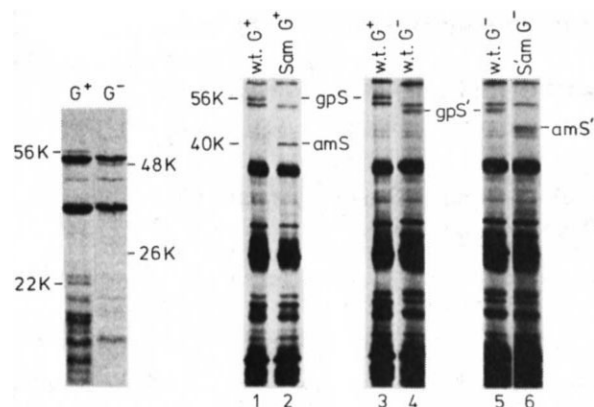


Fig. 2 *a*, Electrophoretic separation of the polypeptides of Mu G(+) and Mu G(-) phage particles¹. The various structural polypeptides indicated are presumed to represent the following gene products (gp): 56K = gp S; 22K = gp U; 48K = gp S'; 26K = gp U'. *b*, Identification of *S* and *S'* gene products in *E. coli* minicells. Minicells were infected with Mu and Mu amber mutants. One hour after infection the minicells were labelled with ³⁵S-L-methionine and the proteins analysed on a 11.5–20% polyacrylamide gradient gel¹³. A Mu polypeptide of *M_r* 56,000 (56K, lane 1) is not synthesized in the minicells infected with Mu *Sam* 1004 (lane 2). The minicell producing strain PC2251, which resulted from a cross between an *E. coli* C donor and the minicell-producing Adler strain (P678–54), was found to be sensitive for G(-) phages. Lane 4 shows the polypeptide pattern of minicells of this strain infected with G(-) phages, compared with a pattern obtained from minicells of DS410 infected with Mu G(+) (lane 3). A 50K polypeptide is synthesized only after G(-) infection. This polypeptide is absent in minicells infected with Mu G(-) amber mutant 2101 (lane 6) or infected with G(-) amber mutant 2102 and 2103 (results not shown).

is non-essential for G(+) phage, as marker rescue of these mutations was observed with recombinant plasmids containing the right part of the G region (pGP202 and 203, Fig. 3b). Therefore, we conclude that there is indeed a region in the G segment which is only essential for G(-) phage. The gene product encoded by this region could be identified in minicells. As can be seen in Fig. 2b, minicells infected with Mu G(+) phage synthesize a 56K polypeptide identified as the *S* gene product (lane 2). This polypeptide is absent when G(-)-sensitive minicells are infected with G(-) phage, but another polypeptide of *M_r* 50,000 (50K, lane 4), comparable with that of the structural *S'* polypeptide, is synthesized instead. This polypeptide is not synthesized in minicells infected with any of the three Mu G(-) amber mutants (lanes 5, 6). These results show that the *S'* gene located in G is essential for G(-) phage only and encodes the structural protein unique for G(-) phage.

To analyse the genetic organization of the G region further, we cloned a Mu DNA fragment containing this region in pBR322. In isolates of this plasmid, pGP56 (Fig. 3a), the G region is found for 50% in the (+) and for 50% in the (-) orientation. Cells containing pGP56 express the genes *R*, *S* and *S'* as measured by complementation of Mu amber mutants.

To distinguish between models A and B (Fig. 1), we have isolated various Tn5 insertions in pGP56, constructed various subclones of this plasmid and tested them for complementation and marker rescue of 'G' amber mutants. Fourteen independent Tn5 insertions were mapped by restriction enzyme analysis in the G region and in regions flanking G (Fig. 3a). Figure 3a also shows the level of complementation of Mu *S* and Mu *S'* amber mutants in strains (either *E. coli* K-12 or *E. coli* C) harbouring pGP56 with the various Tn5 insertions. The results allow the following conclusions. (1) Both *S* and *S'* are expressed from a promoter which is located in α between 900 bp (position 22, *S* and *S'*(+)) and 350 bp (position 44, *S* and *S'*(-)) to the left of the G segment. (2) The entire *S'* gene or *Sv'* is, as postulated, located in the right part of the G segment (in the (+) orientation; see positions 69 and 43). (3) Two Tn5 insertions (44 and 48), located outside the G segment in α , give loss

of expression of both *S* and *S'*. Therefore, these insertions are either in the common part of *S* and *S'* or are located between the promoter and the translation start of *S* and *S'*. (4) The promoter distal end of the *S* gene seems to be located in the vicinity of the *Kpn*I site (975 bp removed from the left inverted repeat), as Tn5 insertions 66 and 42 allow complementation of Mu *S* amber mutants.

To localize both the proximal and distal ends of *S* and *S'*, marker rescue and complementation experiments were performed with subclones of pGP56 (see Fig. 3b). pGP202, which is deleted for the Mu DNA between the two *Hpa*I sites in the G region of pGP56, did not complement Mu *S* or *S'* amber mutants. This result indicates that the C-terminal end of both genes *S* and *S'* stretches beyond the two *Hpa*I sites, located respectively 600 and 900 bp away from the left and right inverted repeats. Marker rescue of the *Sam*1004 mutation was observed with pGP202 and pGP204, whereas both pGP202 and pGP203 rescued the *S'am*2101 mutation. Thus, the *Sam*1004 mutation was mapped in the leftmost 600 bp and the *S'am*2101 mutation in the rightmost 900 bp of the G region. We identified in minicells the amber fragments of *Sam*1004 and *S'am*2101 which represent the translation products of the *S* and *S'* genes up to the amber mutations (Fig. 2). The amber fragment of *Sam*1004 has a molecular weight of 40,000, which requires a coding capacity of 1,100 bp of DNA. Thus, the site of the *Sam*1004 mutation is 1,100 bp removed from the translation initiation point of the *S* gene. The N-terminal end of the *S* gene should therefore be located at least 500 bp to the left of the G region. As 1,500 bp are needed to code for the *S* gene product (56K) this result agrees with the conclusion that the C-terminal end of *S* is located in the vicinity of the *Kpn*I site in the G region. Taking into account the size of the *S'am*2101 amber fragment (45K, Fig. 2), we calculated in a similar way that the *S'* gene should start at least 330 bp to the left of the G region. From the results obtained so far, we conclude that the *S* and *S'* genes share a common part of DNA located outside G in the α region.

To map the promoter proximal end of *S* and *S'* more precisely we identified gene products and truncated proteins synthesized in minicells containing pGP56 and its derivatives containing Tn5 in *S* or *S'* (Fig. 4). If truncated proteins are found, these will represent mainly truncated *S* or *S'* encoded amino acids, for it seems from the DNA sequence of Tn5 (ref. 7) that in all three possible reading frames, translation stop codons occur within the first 30 bp from the ends of the transposon. As is shown in Fig. 4, lane 8, minicells containing pGP56 synthesize the 56K *S* polypeptide and the 50K *S'* polypeptide. Unfortunately, Tn5 encodes polypeptides of reported⁸ *M_r*s 54,000 and 49,000 which co-migrate with *S* and *S'* (Fig. 4, lanes 1, 2). Therefore, it was not possible to show the disappearance of *S*

Table 1 Mapping of the promoter proximal end of the *S* and *S'* genes

Plasmid	Position Tn5 insertion (bp)*	<i>M_r</i> ($\times 10^3$) of truncated proteins†	Distance (bp) from the translation start point to inverted repeat‡	
			<i>S</i>	<i>S'</i>
pGP56::Tn5 no. 33	400 from left IR	37	600	
pGP56::Tn5 no. 3	575 from left IR	43	600	
pGP56::Tn5 no. 63	875 from left IR	54	600	
pGP56::Tn5 no. 69	825 from right IR	48		475
pGP56::Tn5 no. 43	150 from right IR	25		525

* See Fig. 4a legend. IR, inverted repeat.

† Truncated proteins are indicated → in Fig. 4.

‡ Assuming an average molecular weight of .110 for an amino acid. The calculated distance is a maximal value as a contribution of translation into Tn5 has not been taken into account.

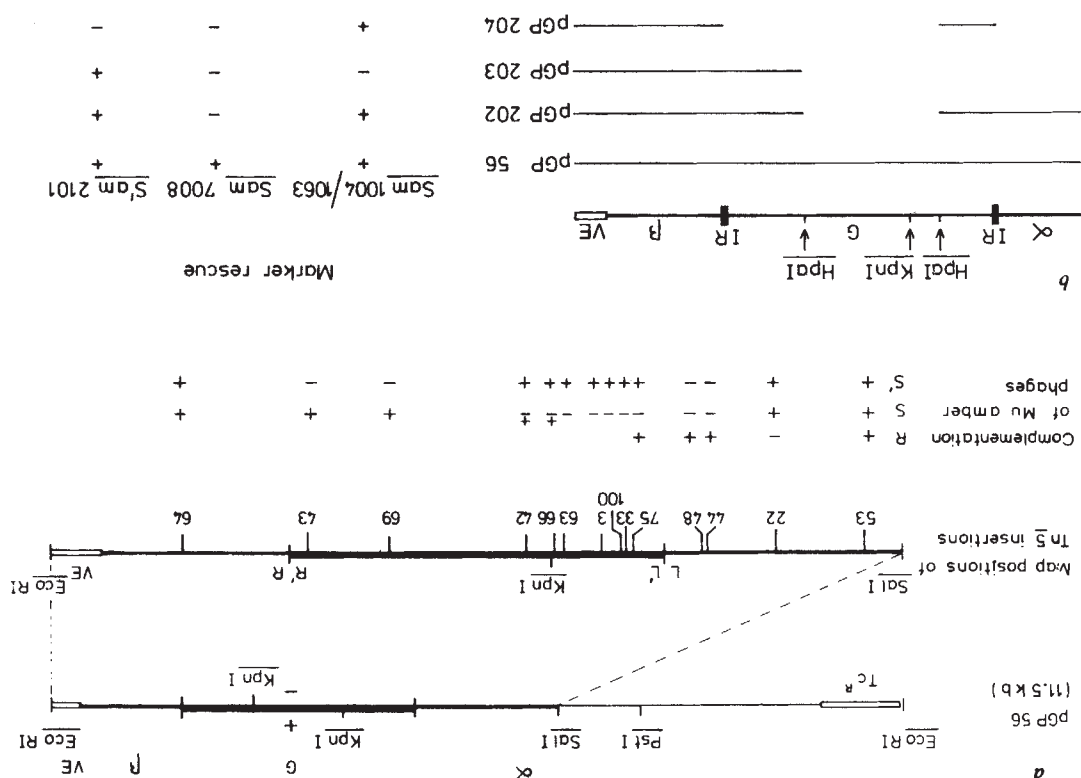


Fig. 3 a, Linear map of plasmid pGP56 (11.5 kb) which consists of Mu DNA (—) cloned in a *Pst*-*EcoRI* fragment of pBR322(—). The Mu DNA comprises a part of α (3 kb), the β segment (3 kb), the β' part (1.5 kb) and 0.4 kb of DNA from the variable ends (VE) of Mu DNA. A comparable plasmid has been described elsewhere⁴. The two possible orientations of the G segment in pGP56 preparations can be visualized by analysis of *EcoRI*/*KpnI* fragments of pGP56 DNA. The map position of various insertions of transposon *Tn5* isolated in the *SalI*/*EcoRI* fragment of pGP56 are indicated in the second line. The solid bar represents the G region and LL' and RR' the left and right inverted repeats. As restriction sites on *Tn5* have been presented¹⁵, the integration sites of *Tn5* could be determined by digestion with restriction enzymes *SalI*, *EcoRI*/*XhoI*, *KpnI* and *KpnI*/*XhoI* (which cuts once in *Tn5*). Digestion shows whether *Tn5* is integrated in the G region. With *KpnI*/*EcoRI* digestion, *Tn5* could be mapped to the left or to the right of the *KpnI* site in G. The distance from the site of integration to the inverted repeats could be calculated by *EcoRI*/*XhoI* and *KpnI*/*XhoI* digestion, as *XhoI* sites in *Tn5* are known precisely¹⁵ and the *KpnI* site was mapped 975 bp from LL'. To measure complementation, *Tn5* were infected with Mu G(+) and without pGP56 or pGP56⁻. *Tn5* were infected with Mu G(+) and without pGP56 or pGP56⁻. After an adsorption period of 15 min at 37 °C, the cells were incubated in the presence of Mu antiserum for 10 min at 37 °C, washed twice and diluted 1,000-fold in L broth. Phage titres were determined after 1 h growth at 37 °C by titration of phage on lawns of *E. coli* K-12, *su*⁻ (for G(+)) phage, or *E. coli* C, *su*⁻ (for G(-)) phage. The level of complementation is indicated + when the phage titres obtained are as high as that of pGP56 (5×10^8 – 1×10^9) and indicated (-) when they are as low as that of bacteria containing no plasmid (5×10^7 – 2×10^8). An aberrant level of Mu *Sam* complementation was obtained with *Tn5* at positions 66 and 42 (1×10^7 and 3×10^7 , respectively). The reason for this low level of complementation is not known. b, Subclones of pGP56. The Mu DNA present on the different plasmids is indicated by a line. As pGP204 is derived from a G(-) molecule of pGP56 the β end is in fact directly linked to the left end of the G region (which is drawn here in the (+) orientation). The construction of the plasmids will be presented elsewhere (R.H.A.P. and P.P., in preparation). To measure marker rescue, *E. coli* K-12, *su*⁻, or *E. coli* C, *su*⁻, with or without a plasmid, were infected with Mu amber mutants with a MOI of 5. Titres of wild-type phage were determined by titration on lawns of *E. coli* K-12, *su*⁻, or *E. coli* C, *su*⁻. The *Sam*1004) or Mu G(-) amber mutants (*Sam*2101), respectively, with a MOI of 5. After an adsorption period of 15 min at 37 °C, the cells were incubated in the presence of Mu antiserum for 10 min at 37 °C, washed twice and diluted 1,000-fold in L broth. Phage titres were determined after 1 h growth at 37 °C by titration of phage on lawns of *E. coli* K-12, *su*⁻ (for G(+)) phage, or *E. coli* C, *su*⁻ (for G(-)) phage. The level of complementation is indicated + when the phage titres obtained are as high as that of pGP56 (5×10^8 – 1×10^9) and indicated (-) when they are as low as that of bacteria containing no plasmid (5×10^7 – 2×10^8). An aberrant level of Mu *Sam* complementation was obtained with *Tn5* at positions 66 and 42 (1×10^7 and 3×10^7 , respectively). The reason for this low level of complementation is not known. c, Subclones of pGP56. The Mu DNA present on the different plasmids is indicated by a line. As pGP204 is derived from a G(-) molecule of pGP56 the β end is in fact directly linked to the left end of the G region (which is drawn here in the (+) orientation). The construction of the plasmids will be presented elsewhere (R.H.A.P. and P.P., in preparation). To measure marker rescue, *E. coli* K-12, *su*⁻, or *E. coli* C, *su*⁻, with or without a plasmid, were infected with Mu amber mutants with a MOI of 5. Titres of wild-type phage were determined by titration on lawns of *E. coli* K-12, *su*⁻, or *E. coli* C, *su*⁻. The *Sam*1004) or Mu G(-) amber mutants (*Sam*2101), respectively, with a MOI of 5. After an adsorption period of 15 min at 37 °C, the cells were incubated in the presence of Mu antiserum for 10 min at 37 °C, washed twice and diluted 1,000-fold in L broth. Phage titres were determined after 1 h growth at 37 °C by titration of phage on lawns of *E. coli* K-12, *su*⁻ (for G(+)) phage, or *E. coli* C, *su*⁻ (for G(-)) phage. The level of complementation is indicated + when the phage titres obtained are as high as that of pGP56 (5×10^8 – 1×10^9) and indicated (-) when they are as low as that of bacteria containing no plasmid (5×10^7 – 2×10^8). An aberrant level of Mu *Sam* complementation was obtained with *Tn5* at positions 66 and 42 (1×10^7 and 3×10^7 , respectively). The reason for this low level of complementation is not known. d, Subclones of pGP56. The Mu DNA present on the different plasmids is indicated by a line. As pGP204 is derived from a G(-) molecule of pGP56 the β end is in fact directly linked to the left end of the G region (which is drawn here in the (+) orientation). The construction of the plasmids will be presented elsewhere (R.H.A.P. and P.P., in preparation). To measure marker rescue, *E. coli* K-12, *su*⁻, or *E. coli* C, *su*⁻, with or without a plasmid, were infected with Mu amber mutants with a MOI of 5. Titres of wild-type phage were determined by titration on lawns of *E. coli* K-12, *su*⁻, or *E. coli* C, *su*⁻. The *Sam*1004) or Mu G(-) amber mutants (*Sam*2101), respectively, with a MOI of 5. After an adsorption period of 15 min at 37 °C, the cells were incubated in the presence of Mu antiserum for 10 min at 37 °C, washed twice and diluted 1,000-fold in L broth. Phage titres were determined after 1 h growth at 37 °C by titration of phage on lawns of *E. coli* K-12, *su*⁻ (for G(+)) phage, or *E. coli* C, *su*⁻ (for G(-)) phage. The level of complementation is indicated + when the phage titres obtained are as high as that of pGP56 (5×10^8 – 1×10^9) and indicated (-) when they are as low as that of bacteria containing no plasmid (5×10^7 – 2×10^8). An aberrant level of Mu *Sam* complementation was obtained with *Tn5* at positions 66 and 42 (1×10^7 and 3×10^7 , respectively). The reason for this low level of complementation is not known.

or S' when *Tn5* was inserted in the respective genes. However, truncated proteins are synthesized in minicells containing pGP56 with *Tn5* inserted at five different positions (Fig. 4, lanes 3, 4, 5, 7, 8). The C-terminal end of the S and S' genes could be mapped, respectively, less than 100 bp removed from *Tn5* no. 63 and *Tn5* no. 69, as their respective truncated proteins are only slightly smaller than the S and S' gene products (Fig. 4, lanes 5, 8). The N-terminal end, or translation startpoint, of S and S' could be calculated from the *M_r* of the various truncated proteins and the map positions of the *Tn5* insertions (Table 1). The position of the N-terminus of the S' gene, ~600 bp removed from the G region, was also determined with pGP202 (Fig. 3b). Minicells containing pGP202 do not synthesize S or S', confirming complementation data, but a 43,000 *M_r* polypeptide (Fig. 4, lane 10). Assuming that this polypeptide represents a truncated S protein, the S' gene should start within 575 bp to the left of the inverted repeat. The results confirm that the start of both S and S' genes is located in the α region 500–600 bp away from the G region. Therefore, S and S' arise by a splicing of a common and an invertible part of DNA, as suggested in model B (Fig. 1).

With regard to U and U' in model B, we have previously been unable to prove genetically the existence of U' and to elucidate the expression of U and U' and their role in host specificity. However, in addition to S and S', pGP56 encodes at least two polypeptides of *M_r* 22,000 and 18,000, which are not encoded by pGP202 (Fig. 4, lanes 9, 10). These polypeptides are good candidates for the gene products of U and U'. The 18K polypeptide may be the U gene product as it is not synthesized in minicells containing pGP56, *Tn5* no. 42 (Fig. 4, lane 6). Genetic experiments failed to prove that *Tn5* no. 42 is indeed integrated in the U' gene, due to the leakiness of *Uam* mutants, although its physical position suggests this. We have postulated that the *gin* gene is expressed, at least in part, from a promoter located in α (ref. 1). However, G inversion is observed with all derivatives of pGP56 described above. Assuming that the observed inversion is caused by *gin*₅, this result suggests that the *gin* gene is predominantly or entirely expressed from a promoter located to the right of *Tn5* no. 43, confirming the data of Kwok *et al.*⁹. We believe the system described here to be the first example of gene splicing by an inversion event and the first example of

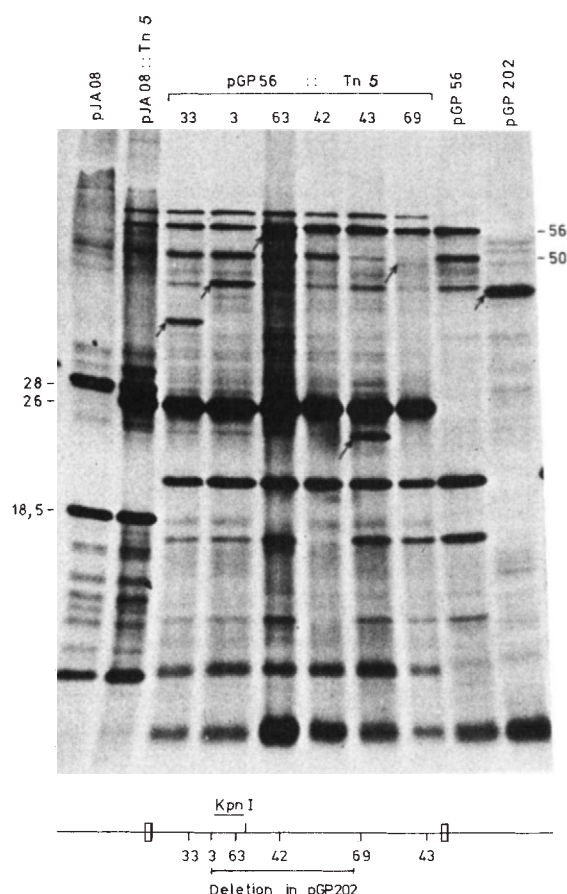


Fig. 4 Autoradiograph showing polypeptides synthesized in minicells isolated from cells containing pGP56, derivatives of pGP56 and plasmids with Tn5 insertions. Minicells were labelled with ^{35}S -L-methionine and the polypeptides separated on a 12.5% polyacrylamide gel¹³. The autoradiograph shows the polypeptide pattern of minicells containing the following plasmids: control plasmid pJA08 (provided by R. Brandsma) (lane 1), pJA08::Tn5 (lane 2), pGP56::Tn5 no. 33 (lane 3), pGP56::Tn5 no. 3 (lane 4), pGP56::Tn5 no. 63 (lane 5), pGP56::Tn5 no. 42 (lane 6), pGP56::Tn5 no. 43 (lane 7), pGP56::Tn5 no. 69 (lane 8), pGP56 (lane 9), pGP202 (lane 10). The *S* gene product (56K), *S'* gene product (50K), β -lactamase (28K)¹³, neomycin phosphotransferase II (26K)⁸ and the product of SSB (18.5K)¹⁷ are indicated. Truncated proteins are indicated by $\rightarrow$.

splicing within the prokaryotic cell. The recombination of a common region to different regions to form variable functional genes is a well known phenomenon in eukaryotes in the assembly of immunoglobulin genes^{10,11}. In the case of G inversion, the variability is in the Sv or the Sv' region. The common region of the S and S' proteins is probably the part which becomes attached to the phage tail, whereas the variable part recognizes the receptor sites of the different hosts. This is now being tested by isolating and mapping mutants of Mu with other host ranges. Although we have shown that S and S' share a common region of DNA in α , this does not directly imply that their respective products are identical at the N-terminus. The calculated N-terminus of genes S and S' differed by ~75–100 bp. This may be due to errors in restriction mapping and/or molecular weight estimation. Moreover, we do not know exactly at which position translation has stopped in the various Tn5 insertions. However, the observed difference may reflect a real difference in length of the Sc part of the two proteins. Therefore, definite proof for the presence of a common part in S and S' at the protein level must await determination of their amino acid sequences.

These results were first presented at the EMBO workshop 'Bacteriophage Mu' (May 1981) and were supported by the nucleotide sequence of the G region as presented by R. Kahmann (Max-Planck-Institute, München) at this workshop. We

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Erratum

In the letter by P. M. Conn *et al.*, *Nature* **296**, 653–655 (1982), the title should read 'Conversion of a gonadotropin-releasing hormone antagonist to an agonist: implication for a receptor microaggregate as the functional unit for signal transduction'. In Fig. 2 the lines labelled *a*, *b* and *c* should be termed (1), (2) and (3) to correspond to the text. In ref. 4 the page numbers should read 264–265, and the journal in ref. 6 is *Endocrinology* **109**, 2040–2045 (1981). In addition the following 'Note added in proof' should have appeared: Additional evidence for the significance of microaggregation comes from the observation of potency enhancement of a GnRH agonist in conditions which favour receptor microaggregation²⁰. In addition, a hormone antagonist has been converted to an agonist by antibody cross-linking²¹.

20. Conn, P. M., Rogers, D. C. & McNeil, R. *Endocrinology* (in the press).

21. Hopkins, C. R., Semhoff, S. & Gregory, H. *Phil. Trans. R. Soc. B* **296**, 73–81 (1981).

Corrigendum

In the letter 'Conversion of the chemical energy of methylmalonyl-CoA decarboxylation into a Na^+ gradient' by W. Hilpert and P. Dimroth, *Nature* **296**, 584–585 (1982), in Fig. 1 the total incubation volume should be 0.67 ml, not 10.67 ml as shown.

BOOK REVIEWS

Sociobiological sins

Michael Ruse

THESE two volumes, which should be read as one, are reports from a conference held in 1980 in Bresanone, Italy. As always with such reports, the quality of contributions is somewhat uneven and not everyone keeps quite so closely to the main themes as they should; in addition they are marked — and marred — by the leaden seriousness of the left. Nonetheless no one is left in any doubt as to the main motivating force behind the books, for, like King Charles's head, in virtually every contribution one topic keeps cropping up, namely the sins of sociobiology. In response to this dreadful phenomenon, what the *Dialectics of Biology* Group offer us is one volume (*Against Biological Determinism*) directed to criticism of the suppositions behind sociobiology. Then, the second volume (*Towards a Liberatory Biology*) turns to possibilities of something better.

The critical volume wastes no time in setting the general theme, with an attack on human sociobiology as socially dangerous. What worries Martin Barker is that sociobiology contains a "potential invitation to a unity of theory and practice in the latest forms of capitalist political economy" (p.26). This is a theme which we have heard sung many times before, most particularly by the Boston-based "Science for the People Sociobiology Study Group". I shall return to it later.

Following more of the same, as well as a brief taxonomy by Hilary and Steven Rose of conventional attitudes to science, we arrive at what I find to be two of the more worthwhile papers, Lynda Birke's and Lesley Rogers's. These two feminists focus on attempts to explain gender identity and sexual orientation in terms of underlying biochemical causes (which in turn are supposedly linked to the genes). The well-known sex researcher, John Money, who must be rueing the day when E. O. Wilson spoke of his work favourably, is singled out for heavy criticism. It is argued that Money bases his claims (specifically, that homosexuality has hormonal causes) on conceptual confusions, as well as inadequate evidence.

The second charge cannot be denied. Most sex researchers put me in mind of philosophers, as they generalize to the whole world from about two cases (which is one more case than Freud, who generalized exclusively from himself). But what of the more interesting claim of conceptual confusion? I am not sure that it holds. Is it really a mistake in logic to suggest that lesbians have "male" type emotions, or

Against Biological Determinism. Pp.184. Hbk ISBN 0-85031-423-2; pbk ISBN 0-85031-424-0. *Towards A Liberatory Biology*. Pp.161. Hbk ISBN 0-85031-425-9; pbk ISBN 0-85031-426-7. The *Dialectics of Biology* Group, general editor Steven Rose. (Allison and Busby/Schocken: 1982.) Each volume hbk £8.95, \$14.95; pbk £4.50, \$8.95.

conversely that male homosexuals have female urges? What really counts in such a situation is the desire and the sex object towards which the desire is directed. The actual mechanics involved seem to be irrelevant: more an incidental by-product of physiology.

Moving along through slight variants on the anti-determinism (chiefly anti-sociobiology) theme in the first volume, we can turn to the more positive *Towards a Liberatory Biology*. Here we find what is perhaps the most sensible essay of the whole set: "Synthesizing Views about the Origin of Behaviour" by Patrick Bateson. The author perceptively points to some of the problems facing the student of behaviour, particularly those arising from the need to sort out innate from environmental factors. I suspect that Bateson must have felt somewhat uncomfortable at the Bresanone conference, for he calmly assumes that orthodox biologists have indeed made important advances in our understanding of behaviour. For instance, he praises Maynard Smith's use of game theory as a tool for understanding aggression, although elsewhere this is criticized as yet one more excursion into the realm of the unfalsifiable.

Since sociobiology, with its emphasis on natural selection, is so very much part of the whole Darwinian paradigm, the most radical attack is obviously one which goes right to the heart of Darwinism itself, hoping to put forward a new theory of evolution. This is the theme of several of the contributors to the second volume, as they urge upon us various neo-Lamarckian and neo-vitalist alternatives. But I doubt that the Ernst Mayrs of this world need worry too much yet. The critics base their case on some fairly worn arguments against natural selection, together with some incredible rewritings of history. I simply do not know how Gerry Webster and Brian Goodwin ("History and Structure in Biology") can accuse Darwin of being hostile to Cuvier's ideas or to the rational morphologists' "plan of creation". In

fact, I would say that, in his thoroughgoing teleology, Darwin owes more to the non-evolutionist Cuvier than he does to the evolutionist Lamarck. Moreover, the very crux of Darwin's work was his incredible sensitivity to the morphologists' ideas, which he learnt from people like Richard Owen. Darwin's genius was to combine both form and function into one synthetic theory — form through common descent and function through natural selection. Furthermore, to say that Darwin was "firmly in the empiricist/positivist tradition" (p.104) is to ignore entirely the influence on Darwin of such rationalist thinkers as William Whewell, and the difficulties that full-blown empiricists such as Huxley had with Darwin's selection mechanisms.

All in all, I am afraid that I find these volumes unprepossessing; but let me make three concluding points. First, I agree entirely with the DBG that a blind reductionism, aiming to explain everything in terms of the Hardy-Weinberg law — or even worse, some simplistic law of physics — is the last thing that biologists should aim for. Anyone who says that life and its problems is just a set of molecules is either a fool or a liar. But, second, there is no evidence that sociobiology is committed to such a gormless programme of reductionism, despite the outlandish statements of some of its more enthusiastic proponents. Sociobiologists continue to deal with *biological* questions; moreover, the last thing that sociobiology does is to exclude methods and findings from other disciplines, such as psychology and sociology. Rather, the social sciences are given a crucial role in the overall picture. Thus, for instance, suppose that there is something in the sociobiological claim that incest barriers have a genetic foundation. This says nothing about the role which genotypes have in causing such barriers. Instead, all sorts of questions are asked (and answers demanded) about the ways in which close contact with siblings in early childhood lead to anti-sexual imprinting. And who is to answer these questions but social scientists?

This conclusion is precisely what one would expect, given that sociobiology lies so firmly within the Darwinian tradition. Darwinism has always claimed that evolution is a function of heredity in interaction with the environment. A purely biological (meaning especially a purely genetic) determinism is meaningless to the Darwinian.

Third and finally, let me speak to the concern articulated by Martin Barker, but I think behind nearly all of the opposition to sociobiology and like enterprises. When all is said and done, is it not really the case that sociobiology is merely right-wing ideology dressed up to look like genuine science? One would have to be insensitive not to recognize this as a genuine concern, or to deny that genetic theories of human behaviour have been (and still are) used to "support" some pretty horrible social doctrines. But it is simply not true to claim unequivocally that all genetic theories are apologia for the worst excesses of Western capitalism, any more than it would be true to claim that all environmentalist theories are as ideologically pure as the driven snow. Indeed, some thoroughly dreadful practices have been pushed by people who claim that all we need is a little of the right social conditioning.

In short, I remain unconvinced that sociobiology is the inherently evil thing supposed by the DBG. No doubt the members of the DBG will remain equally unconvinced of what I say. But could I make one request? Do not let us degenerate into accusations that the other side is responsible for the rise and success of Creationism — as the cover of one of these books suggests. There is simply no causal connexion between sociobiology and Creationism, and to pretend otherwise is gratuitously insulting. For all our differences, do not forget that we are all striving, painfully, to see the light. □

Michael Ruse is a Professor in the Departments of History and Philosophy at the University of Guelph. His most recent book is Darwinism Defended (Addison-Wesley, 1982).

Journals' review issue 1982

On October 7th *Nature* will publish a second review supplement devoted to science journals. Last year's supplement, covering journals first published between January 1978 and May 1980, appeared in *Nature* 293, 341-369; see p.343 of that issue for details.

Criteria for inclusion of a journal in the 1982 issue are that:

- the first number appeared, or the journal was re-titled, between June 1980 and May 1981;
- it is published at least three times a year;
- the main language used is English.

Broadly, periodicals of professional interest to scientists will be considered for review, with the exception of abstracts' journals.

In addition it is hoped to cover publicly available newsletters, first published between January 1978 and May 1981, in that issue.

Publishers and societies are invited to submit four sample issues of periodicals satisfying the above criteria, including the first and most recent numbers, to the Review Editor, *Nature*, 4 Little Essex St, London WC2R 3LF, England (London 836 6633 ext 2570) as soon as possible.

The biological roots of personality

Anthony Gale

A Model for Personality. Edited by H. J. Eysenck. Pp.287. ISBN 3-540-10318-X/0-387-10318-X. (Springer-Verlag: 1981.) DM78, \$37.20.

AT THE dinner last summer to celebrate the publication of his *Festschrift*, Hans Eysenck declared himself to be confused. This unusual state of mind resulted from a paradox. The same scientific thinking which had led him to reject fascism in his youth had created enemies in his old age. His analysis of IQ differences between ethnic groups, and his insistence that biological factors account for differences between individuals, have led to accusations of racism. Eysenck-bashing has become a popular sport, not only on the campus, but in scientific journals. He only needed to look to his own writings for an answer to the paradox; frequently he talks of the *zeitgeist*, the prevailing scientific fashion which favours some approaches and castigates others. And he has never been afraid to profess unpopular views, whether it be to attack psychoanalysis or to accuse his fellow psychologists of sloppy thinking.

In *A Model for Personality* Eysenck invites his critics to do their worst. His theory of the biological basis of extraversion, and the data which support it, are laid out before us, warts and all. He sees himself in a long line of biological theorists, stretching back to the Greek physician, Galen. The argument is straightforward: systematic studies of personality reveal two common factors, extraversion-introversion and neuroticism-stability; and their ubiquitous appearance implies that they are *given* by nature. If they have biological roots, we expect them to be normally distributed across the population, to be transmitted by genetic mechanisms, expressed in brain function, and adaptive in governing the interaction of the individual with his physical and social environment. Each of the contributors to the book (all are internationally established authorities) deals with one of these aspects of the theory.

The reader should recognize that, for many psychologists, the establishment of links between genetics, biology, learning, and the way people think and interact socially involves a tremendous imaginative leap into the unknown, for it presupposes that all the philosophical problems raised by the Mind-Body relationship will ultimately be resolved. Some of the tricks, which involve a shift between diverse domains of description, are truly remarkable. For example, a 24-item *paper and pencil* test about how you feel in different situations ("Would you rather stay at home, or go to a dull party?") enables successful prediction of *electrical* properties of the brain. Eysenck believes,

as did Pavlov, that nervous systems *qua* nervous systems, have properties which determine the ways in which the organism acts upon and responds to the environment. *The Dynamics of Anxiety and Hysteria* (Routledge & Kegan Paul, 1957) and *The Biological Basis of Personality* (Thomas, 1967) showed how Eysenck's theory could find operational expression in the form of systematic laboratory experiments. This *rapprochement* between traditional experimental psychology and personality theory is illustrated by his son Michael's chapter, reviewing studies of personality, learning and memory.

The penultimate chapter, by Jeffrey Gray, offers a savage critique of the theory. He claims that Eysenck's selection of a particular mathematical solution to factor data does not fit the facts, that every data set supporting the theory is matched by a contradictory set, that the 1957 and 1967 versions generate different and even conflicting predictions, and that the key instrument of measurement (the Eysenck Personality Inventory) has undergone surreptitious changes over the years. Only Eysenck could invite a colleague (possibly his successor at the Institute of Psychiatry?) to write such a provocative and thoroughgoing critique of his own theory.

This is a very useful, balanced and sensibly compiled record of Eysenck's progress in this his retirement year. It is ironic that in the 1980s there is a move towards a more biological perspective: the pendulum is swinging back in Eysenck's direction. □

Anthony Gale is Professor of Psychology at the University of Southampton. He is co-editor of The Biological Bases of Personality and Behaviour (Hemisphere Press, 1982) and Psychology and People: A Tutorial Text (BPS-Macmillan, 1982).

Chariots of water

M. Ian Phillips

Thirst. By Barbara J. Rolls and Edmund T. Rolls. Pp.194. Hbk ISBN 0-521-22918-9; pbk ISBN 0-521-29718-4. (Cambridge University Press: 1982.) Hbk £15, \$29.50; pbk £5.50, \$10.95.

EVERY year in London on the neutral waters of the Thames there is a race between a row-boat from Cambridge University and one from Oxford. I was reminded of this when asked to review *Thirst* by Barbara Rolls and Edmund Rolls from Oxford University, since a year ago I

reviewed *The Physiology of Thirst and Sodium Appetite* by James Fitzsimons from Cambridge University (*Science* 208, 711; 1980).

This latest response from Oxford in the race for dominance of the water intake field is a fast-moving, sometimes too brief but nonetheless highly readable account of our present knowledge of thirst. It is not as erudite as the volume by Fitzsimons — it is less than half the size for one thing — but it is a book that one could recommend to students of physiological psychology and researchers newly attracted to the field. It covers a comprehensive list of topics and as an introductory text it is excellent. What it lacks for the researcher actively involved in these studies is the depth of sources and an accounting of all available information. For example, the authors avoid covering the brain angiotensin system in detail by dismissing it as being controversial. Perhaps that attitude is the better part of valour, but in consequence much recent data are overlooked.

Since most of the interest in the subject can be attributed to the discovery that injections of angiotensin II stimulate thirst, it is appropriate that Barbara Rolls is the senior author of this text. It was she, with Fitzsimons, who first showed that effect of angiotensin II intravenously and shortly afterwards intracranially. Edmund Rolls adds his unique expertise in the understanding of central mechanisms of thirst in primates. It is a winning combination for a work that will appeal to those interested in the physiology of motivation.

The book is profusely illustrated with clear pictures, almost one to a page. The material presented is a readable summary of the progress that has been made in the study of thirst and particularly since the discovery of the effects of angiotensin II in 1969. It is apparent, however, that the race is not over because the control of drinking under normal physiological conditions has not yet been established; the authors say that involvement of angiotensin in thirst may only be in emergencies. As a review of the field, the book enables one to see that advances have been made with relatively simple techniques. The flow of experiments presently is towards more precise localization of receptors and more accurate descriptions of the brain pathways involved. In that respect, thirst research is not yet far from the starting line.

The book does show that there is sufficient data for a course in thirst and for an active field of research. There is certainly room for the two volumes on water intake without causing hyper-volumia and, as far as competition between the two books goes, the winner seems to be Cambridge since its University Press is the publisher of both. □

M. Ian Phillips is Chairman of the Department of Physiology at the University of Florida, Gainesville.

Genes through the looking glass

P.H. Williams

Gene Function: E. coli and Its Heritable Elements. By Robert E. Glass. Pp.487. Hbk ISBN 0-7099-0081-3; pbk ISBN 0-7099-0082-1. (Croom Helm/University of California Press: 1982.) Hbk £19.95, \$45.60; pbk £9.95, \$22.80.

WHEN, several years ago, I embarked upon post-graduate research in microbial genetics, the pre-eminent textbook of the field was *The Genetics of Bacteria and their Viruses* by William Hayes. To a newcomer like myself, Hayes was indispensable, offering all there was to know about molecular genetics in an authoritative, well-referenced, easily readable package. It was with great regret that I watched that book drift slowly, but inevitably, out of date.

Gene Function by Robert Glass is, to use Hayes's description of his own work, "a rather advanced text book". It covers much the same ground as Hayes, and is aimed at the same type of audience, namely at advanced undergraduates, and at researchers in the field at every level. Only a few authors since Hayes have successfully abridged the monumental mass of *Escherichia coli* research into a single informative but highly readable volume. In my opinion Robert Glass has made a creditable attempt.

Gene Function, however, is not merely Hayes updated. Over and above the incorporation of the wealth of knowledge accumulated over a decade and a half, Glass's book has an entirely different viewpoint which reflects the backgrounds and attitudes of those who have more recently entered and contributed to the field. Hayes began his book with an introduction to genetic principles, and then developed the theme of bacteria and bacteriophage as genetic systems. Glass, on the other hand, writes as a biochemist, beginning with an overview of the structure and biological role of nucleic acids at the molecular level (or rather a preview, since these are covered in detail later), before outlining elements of microbial physiology and metabolism essential to a full comprehension of experimental methods.

In the preface to his book the author thanks a colleague for "a 'sensible' title". It is a little surprising that a volume devoted exclusively to one organism should presume to claim for itself the title *Gene Function*. However, this book is about genes and the way they function in that particularly convenient little bag known as *E. coli* — simple genes, perhaps; organized and regulated differently from those of eukaryotes, certainly; but the strong implication is that knowledge of the molecular wonderland of *E. coli* genes will form a firm basis for the study of genes in any other organism. Nonetheless, the title still worries me a little.

Gene Function is well researched, adequately referenced and nicely balanced in terms of breadth of material and depth of detail. In general it is clearly written, although extensive cross-referencing tends to destroy the reader's train of thought at times. The frequent use of footnotes and parentheses in the text irritated me somewhat, and I confess that I found the index almost impossible to use. However, these are quite minor quibbles, and, except for the last point, did not seriously detract from my enjoyment of the book. *Gene Function* may not, perhaps, be as fondly remembered 15 years hence as Hayes's book is now, but there is no doubt that it is an important and useful addition to the book-shelves of today's molecular geneticists. I hope it can be regularly updated without losing any of the evident enthusiasm of its author. □

P. H. Williams is a Lecturer in the Department of Genetics at the University of Leicester.

Space-time through time

Paul Davies

The Science of Space-Time. By Derek J. Raine and Michael Heller. Pp.255. ISBN 0-912918-12-8. (Pachart Publishing, Tucson, Arizona: 1981.) \$24.

It is curious the way that certain ideas and concepts in science exercise a wide and seemingly disproportionate fascination. These include the measurement paradoxes of quantum theory, and the origin of time's mysterious "arrow". Another is Mach's principle. Scientists return to it again and again. Now, for the first time, a comprehensive treatment of Mach's principle is available in a book that can be profitably read by those with only a basic knowledge of space-time physics.

The basic idea of Mach's principle is that the property of inertia in a material body has its origin in cosmology. A rotating planet, for example, feels centrifugal stresses and bulges at the equator. But visually the Earth's rotation is deduced by "watching the stars go round". So, are these two radically different phenomena — the experience of centrifugal bulging and the whirling of the stars — in some way connected? Are rotations (and other types of accelerated motions) purely relative to the background framework of far-flung galaxies?

Einstein at first thought so, and Mach's work deeply influenced his development of the theory of relativity. In 1916, on Mach's

The Biology of the Coccidia

Edited by Peter L. Long

The Biology of the Coccidia is the updated version of *The Coccidia* edited by the late Dr Hammond and Dr Long. Since the publication of the first edition there has been much new research on this group of parasites including the discovery that some species are parasites of man as well as other animals. This book has been thoroughly revised and includes a new chapter on chemotherapy and new details of life cycles of several species of Sarcocystis and Toxoplasma. There are several new contributors. The contributors are all leading authorities in the field.

£45 boards 512 pages
Publication May

Plant Growth Curves

A functional approach to plant growth analysis

Roderick Hunt

A review of the theory, practice and applications of the use of fitted mathematical functions in plant growth analysis. The approach taken is very broad and includes an extended coverage of the philosophical and scientific links between this topic and related fields of activity in plant science.

£8.75 paper 240 pages
Publication June

Optima for Animals

R. McNeill Alexander

Optimization theory is the branch of mathematics concerned with finding those structures and behaviours that are in some sense the best possible, and is therefore a very appropriate tool for trying to discover why animals have evolved in particular ways.

£5.25 paper 120 pages
Publication June



Edward Arnold

41 Bedford Square
London WC1B 3DQ

death, Einstein wrote a tribute to him. But in spite of this Machian input, a clear-cut manifestation of Mach's principle failed to emerge in any very obvious way from relativity theory. Over the decades, many theoretical physicists have struggled to find formulations of Mach's principle that would mesh easily with either the theory of relativity, or some close variant. It is a task as yet unfinished, but it remains as compelling as ever. At issue is one of the fundamental properties of space-time structure, and the nature of motion.

This timely and most welcome book contains a discussion of the evolution of the space-time concept from Aristotle to Einstein (and beyond), and presents a detailed and up-to-date analysis of Mach's principle in a modern setting. The authors conclude that "At best, Mach's principle has been expressed in general relativity as a selection rule. To go beyond this . . . one may have to give up general relativity".

However, this book is far from a

catalogue of failures. It is a comprehensive and accurate survey of the physics of space and time and of the philosophical overtones which accompany it. The theory of relativity, both the special and general versions, obviously plays a central role in these ideas, and the reader will find discussions of black holes and details of gravitation experiments as well as a careful introduction to the more elementary aspects of space-time structure.

Mach's principle is an intriguing context in which to learn relativity and space-time physics, as well as an end in itself. I can thoroughly recommend this book to undergraduates learning general relativity, as well as to researchers who share the authors' fascination with one of science's age-old mysteries. □

Paul Davies is Professor of Theoretical Physics at the University of Newcastle upon Tyne. His most recent book (with N.D. Birrell) is Quantum Fields in Curved Space (Cambridge University Press, 1982).

The mixed blessing: oxygen in biology

Barry Halliwell

Oxygen and Living Processes: An Interdisciplinary Approach. Edited by Daniel L. Gilbert. Pp.401. ISBN 3-540-90554-5/0-387-90554-5. (Springer-Verlag:1981.) DM135, \$61.40.

THIS colourless, odourless gas is an extreme fire hazard and is very toxic to some organisms at minute concentrations. Its toxicity to human beings is much slower-acting, but nevertheless over a period of many years it produces a progressive oxidative deterioration that results inevitably in death. Only the swim-bladders of certain fishes can tolerate it at high concentrations, although turtles and crocodiles are fairly resistant to its toxic effects unless they are placed in warm water.

The above description, using information taken from this book, applies of course, to oxygen. Oxygen is essential for efficient energy production by oxidation of foodstuffs in aerobic animals, but only its peculiar chemistry protects us from instant "spontaneous" combustion. The same chemistry dictates that the oxygen reduction accompanying substrate oxidation must proceed via partially reduced oxygen intermediates on the pathway to water. Such intermediates as superoxide and hydroxyl radical are particularly noxious and so aerobic cells are equipped with many defences against them, including superoxide dismutase, catalase, glutathione and/or ascorbate peroxidases and vitamin E. The cytochrome oxidase complex of mitochondria is carefully designed not to allow the escape of such intermediates from its active site.

As its title declares, this book is indeed an interdisciplinary approach to oxygen. All of the items I have mentioned are covered in detail, and in addition there are chapters on photosynthetic oxygen production, the geological history of the oxygen in the Earth's atmosphere, oxygen-carrying pigments, kinetics of oxygen diffusion, the history of the discovery of oxygen, and the medical uses (and abuses) of the gas, covering blindness in babies, pulmonary oxygen toxicity and hyperoxygenation in the treatment of gas gangrene and cancer of the head and neck. The contributions are well-written, all of them by experts in specific fields, and the book has been produced in an attractive style with the minimum of errors.

I do have some minor niggles, however. Much of Chapter 1, a history of the discovery of oxygen, is merely an over-condensed — and rather boring — list of names and dates; for example, it is impossible to do justice to the complex physiology expounded by Galen in a few lines. In Chapter 6, on photosynthesis, I doubt whether non-biologists will really understand what exactly are photosystem I, photosystem II and Q. In addition, the order of the chapters is sometimes a bit illogical.

These comments are not meant to detract from what is an excellent book. It is truly "everything you wanted to know about oxygen, but didn't know whom to ask". □

Barry Halliwell is a Lecturer in Biochemistry at King's College, University of London, and author of Chloroplast Metabolism (Clarendon/Oxford University Press, 1981).

ANNOUNCEMENTS

Awards

The French National Order of the Legion of Honor has been awarded to University of California, San Francisco clinical professor **Piero Mustacchi** for 25 years of prominence in professional activity, in particular for developing academic and medical links between the University of California and universities in France and French-speaking Africa.

Professor William H. Thorpe (University of Cambridge) has been presented with the annual prize of the Fyssen Foundation for his research in animal behaviour.

Dr Prescott L. Deininger (Louisiana State University Medical Center in New Orleans) and **Dr Jeffrey W. Williams** (Ohio State University) have been selected to receive the Boehringer Mannheim Biochemicals travel awards in molecular biology and in enzymology.

The British Society of Rheology has awarded its annual award to **Professor Joachim Meissner**, **Dr Hans Martin Laun**, **Dr Helmut Munstedt** and **Dr Manfred Wagner** for work in the development of elongational rheometry.

Five prizes have been awarded to young Weizmann Institute scientists: the Somach Sachs Memorial Award to **Dr Itamar Procaccia** for studies on rates of chemical reaction near phase transition points; the Sarah Zinder Leedy Memorial Award to **Dr Gideon Schechtman** for work on geometric structure of Banach spaces; the Samuel Yaroslavsky Memorial Award to **Dr Abraham Shanzer** for work on synthesis of large, ring-shaped organic materials; the E.D. Bergmann Award to **Dr Michael Levitt** for studies of conformation and structure of macro-molecules; the M. Levinson Prize to **Dr Mordechai Milgrom** for work on emission of spectral lines with changing wavelengths by the astronomical object SS 433.

Twenty Harkness Fellowships tenable for between 12 and 21 months are offered each year. The award includes return fares to the United States, living and family allowances, travel in America, tuition and research expenses, equipment allowance and health insurance. Candidacy is open to men and women in any profession or field of study, who are citizens of the UK and have received both secondary schooling and further education (or equivalent professional experience in lieu of further education) wholly or mainly in the UK. Candidates must be between 21 and 30 years of age on 1 September 1983, unless qualified in medicine or employed in the Civil Service or the media, in which cases the upper age limit is 33. For application forms (available only to candidates) send a

self-addressed envelope carrying 29p postage, and measuring not less than 10 by 7 inches, to The Harkness Fellowships (UK), Harkness House, 38 Upper Brook Street, London W1Y 1PE. Forms will not be posted from the office after 7 October, 1982.

In recognition of his contributions to the understanding of the meaning of evolution, the history of life, animal taxonomy and mammalian systematics, The Peabody Museum of Natural History, Yale University has established the George Gaylord Simpson Prize in celebration of his 80th birthday, 16 June 1982. The prize will be presented annually by the Peabody Museum to a young author (under 35) of an outstanding paper in the above areas of science. Applications to the Director, Peabody Museum of Natural History c/o Yale University, PO Box 6666, 170 Whitney Ave, New Haven, Connecticut 06511, USA by 31 December 1982.

Appointments

The National Academy of Sciences has announced the election of the following foreign associates: **Nicola Cabibbo** (theoretical physics, University of Rome); **Shmuel Eisenstadt** (sociology, Hebrew University of Jerusalem); **Paul Fraisse** (experimental psychology, University of Paris V); **Marianne Grunberg-Manago** (CNRS, Paris, and biochemistry, University of Paris VII); **Hua Luogeng** (mathematics, Chinese Academy of Sciences); **Il'ya Mikhailovich Lifshitz** (theoretical department, Institute for Physical Problems, Moscow); **Jacques F.A.P. Miller** (experimental pathology, The Walter and Eliza Hall Institute of Medical Research, Melbourne); **Martin J. Rees**, (theoretical astronomy, University of Cambridge); **Ralph Riley**, (Agricultural Research Council of the UK); **John Maynard Smith** (biology, University of Sussex); **Takashi Sugimura** (molecular biology, Tokyo University); **Tsuneo Tomita** (medicine, Keio University, Tokyo).

Professor Emanuel Mazon, has been named as the first incumbent of the Frank W. Conside Chair in Hydrological Research at the Weizmann Institute of Science, Rehovot.

Paul C. Martin will occupy the newly established chair at Harvard University: the John Hasbrouck Van Vleck Professorship of Pure and Applied Physics.

Dr William Taylor present director of the University of London Institute of Education has been appointed principal of the University of London from 1 September 1983 in succession to Mr J.R. Stewart who will be retiring.

Meetings

21-24 June, **Environment 82**, Stockholm (Environment 82, Ministry of Agriculture, S-103 33 Stockholm, Sweden).

28 June-2 July, **Meeting on The Monsoon Climate Programme**, Geneva (WMO Secretariat, Geneva, Switzerland).

28-30 June, **Nordic Congress of Pathological Anatomy and Cytology**, Copenhagen (NOPAC '82 Secretariat, Institutterne, Frederik den V's vej 11, DK-2100 Copenhagen O, Denmark).

29 June, **Design and Safety of the Sizewell Reactor**, London (The Royal Society, 6 Carlton House Terrace, London SW1, UK).

29-30 June, **Food and People**, London (The Secretary BNF, 15 Belgrave Square, London SW1, UK).

30 June, **Energy Conservation, Economic Growth, and Employment**, London (Centre for Energy Studies, Polytechnic of the South Bank, Borough Rd, SE1, UK).

30 June-1 July, **Trace Elements in Animal Production and Veterinary Practice**, York (BVA, 7 Mansfield St, London W1, UK).

28 June-2 July, **Biomedical Writing**, Harvard (Office of Continuing Education, Harvard School of Public Health, 677 Huntington Ave, Boston, Massachusetts 02115, USA).

5-7 July, **Distributed Computing Systems**, Strathclyde (Mr F. Chambers, Logica, 64 Newman St, London W1, UK).

5-9 July, **Concrete Mix Design**, London (Cement and Concrete Association, Fulmer Grange, Fulmer, Slough, UK).

6-9 July, **North Atlantic Ocean Stations**, Geneva (World Weather Watch Dept, WMO, Geneva, Switzerland).

8-9 July, **Physical Techniques in Cardiological Imaging**, Southampton (Dr M. D. Short, Dept of Medical Physics, University College Hospital, London WC1, UK).

9-10 July, **Genetics Cancer-Environment**, Monaco (Institut Pasteur de Lyon, 77 rue Pasteur, 69365 Lyon Cedex 2, France).

12-16 July, **Environment and Safety Risk Management**, Massachusetts (Director of the Summer Session, Room E19-356, MIT, Cambridge, Massachusetts 02139, USA).

13-16 July, **Proteins and Nucleic Acids in Plant Systematics**, Bayreuth (Prof. Dr U. Jensen, Dept of Plant Ecology and Systematics, University of Bayreuth, PO Box 3008-D-8580 Bayreuth, FRG).

14-15 July, **Quantitative Structure Activity Relationships in Taste and Olfaction**, Reading (Dr M. G. Lindley, Tate & Lyle Group R & D, PO Box 68, Whiteknights, Reading, UK).

14-16 July, **Ions, Cell Proliferation and Cancer**, Lake Placid (Dr W. L. McKeehan, W. A. Jones Cell Science Center, Old Barn Rd, Lake Placid, New York 12946, USA).

- 15-16 July, **Climatic Effects of Increasing Atmospheric Carbon Dioxide**, East Anglia (Dr T. M. L. Wigley, Climatic Research Unit, University of East Anglia, Norwich, Norfolk, UK).
- 19-23 July, **Basic Cell and Organ Culture Course**, Boston (Course Administrator, Cell Culture Research Unit, Dept of Anatomy and Cellular Biology, Tufts University School of Medicine, Boston, Massachusetts 02111, UK).
- 19-22 July, **Computer Aided Design and Manufacture**, Manchester (S. Mayhew, Scientific and Technical Studies, Norwich House, 11/13 Norwich St, London EC4, UK).
- 20-22 July, **Fetal Antigens and Cancer**, London (The Ciba Foundation, 41 Portland Place, London W1, UK).
- 23-24 July, **Immune Complexes: Formation, Biological Properties and Clinical Aspects**, Nottingham (Dr W. G. Reeves, Dept of Immunology, University Hospital, Nottingham, UK).
- 10 August, **Milestones and Trends in Polymer Science**, Michigan (Dr J.K. Rieke, Chemical Company, Midland, Michigan 48640, USA).
- 23-28 August, **Stress Effects on Photosynthesis**, Diepenbeck (Dr R. Marcelle, Laboratory of Plant Physiology, Research Station of Gorsem, B-3800 Sint Truiden, Belgium).
- 23-27 August, **9th Annual European Geophysical Society Meeting**, Leeds (Royal Meteorological Society, James Glaisher House, Grenville Place, Bracknell, Berks, UK).
- 23-26 August, **Powder Mixing Technology**, Central New Jersey (The Center for Professional Advancement, PO Box H, East Brunswick, New Jersey 08816-0257, USA).
- 29 August-4 September, **21st International Horticultural Congress**, Hamburg (Hamburg Messe und Congress GmbH Abt. Öffentlichkeitsarbeit, Postfach 30 23 60, 2000 Hamburg 36, FRG).
- 20-24 September, **Molecular Crystal Symposium**, Quebec (D. Chartrand, National Research Council Canada, Ottawa, Canada K1A 0R6).
- 21-23 September, **Radiation Curing**, Illinois (S. Buhr, Technical Activities Dept, Society of Manufacturing Engineers, 1 SME Drive, PO Box 930, Dearborn, Michigan 48128, USA).
- 21-24 September, **Ceramic-Metal Joining**, Amsterdam (The Center for Professional Advancement, Postbus 19865, 1000 GW Amsterdam, The Netherlands).
- 21-24 September, **Pteridines and Folic Acid Derivatives**, St Andrews (Prof. H.C.S. Wood, Dept of Pure and Applied Chemistry, University of Strathclyde, 295 Cathedral St, Glasgow, UK).
- 21-24 September, **Wind Energy Systems**, Stockholm (BHRA Fluid Engineering, Cranfield, Bedford, UK).
- 21-25 September, **British Veterinary Association, Centenary Congress**, Reading (BVA, 7 Mansfield St, London W1, UK).
- 22-24 September, **601st Meeting of The Biochemical Society**, Aberdeen (The Meetings Officer, The Biochemical Society, 7 Warwick Court, London WC, UK).
- 22-26 September, **Biophysical Aspects of Receptor Structure and Function**, Portorose (Prof. D. Hadzi, Bopis Kidric Institute of Chemistry, POB 380, 61001 Ljubljana, Yugoslavia).
- 23 September, **Fluids in Metamorphism**, Glasgow (Dr M. Brown, Dept of Geology and Physical Sciences, Oxford Polytechnic, Oxon, UK).
- 23-24 September, **Choice of Material for Condenser Tubes and Plates and Tube and Tightness Testing**, Avignon (Societe Francaise D'Energie Nucleaire, 48 rue de la Procession, F-75724 Paris, Cedex 15, France).
- 27 September-1 October, **1st International Congress of Neuroimmunology**, Lake Maggiore (Dr P.O. Behan, Institute of Neurological Sciences, Southern General Hospital, 1345 Govan Rd, Glasgow, UK).
- 28-30 September, **The Geological Evolution of the Eastern Mediterranean**, Edinburgh (Dr A.H.F. Robertson, University of Edinburgh, Grant Institute of Geology, West Mains Rd, Edinburgh, UK).
- 27 September-1 October, **Physical Chemistry of Transmembrane Ion Motions**, Paris (Dr C. Troyanowsky, Societe de Chimie Physique, 10, rue Vauquelin, F75321 Paris, Cedex 05, France).
- 28-29 September, **Particle-Fluid Separation in Offshore Engineering**, Middlesbrough (Dr G.S. Bainbridge, Dept of Chemical Engineering, Teesside Polytechnic, Borough Rd, Middlesbrough, Cleveland, UK).
- 29 September-1 October, **Biotechnology in Clinical Chemistry**, Cambridge (Dr C.P. Price, Dept of Clinical Biochemistry, Addenbrooke's Hospital, Hills Rd, Cambridge, UK).
- 30 September-2 October, **Deburring and Surface Conditioning**, New Orleans (J. Slaughter, SME, 1 SME Drive, PO Box 930, Dearborn, Michigan 48128, USA).
- 4-6 October, **Technology for Space Astrophysics — The Next 30 years**, Danbury (N. Geril, Perkin-Elmer Corp, 100 Wooster Heights Rd, Danbury, Connecticut 06810, USA).
- 4-7 October, **Hormones and Cell Regulation**, Alsace (Dr R. Denton, Dept of Biochemistry, University of Bristol, Medical School, Bristol, UK).
- 5-8 October, **Leaf Protein Research**, Aurangabad, (Dr N. Singh, Central Food Technological Research Institute, Mysore 570 013, India).
- 6-8 October, **The Chemical Industry and the Environment in the 1980s**, London (Society of Chemical Industry, 14 Belgrave Square, London SW1, UK).
- 12 October, **Radiological Protection and Home Defence**, London (Prof. J.H. Martin, Dept of Medical Biophysics, Dundee University, Dundee, UK).
- 13-15 October, **Energy: Money, Materials and Engineering**, London (The Institution of Chemical Engineers, George E. Davis Building, 165-171 Railway Terrace, Rugby, UK).
- 17-22 October, **Congress of Allergy and Clinical Immunology**, London (XIIACACI, Conference Associates ICACI, 34 Stanford Rd, London W8, UK).
- 18-20 October, **New Spectroscopic Methods for Biomedical Research**, Columbus, (K.L. Waite, Battelle's Columbus Laboratories, 505 King Ave, Columbus, Ohio 43201, USA).
- 18-20 October, **Radar '82**, London (The Institution of Electrical Engineers, Savoy Place, London WC2, UK).
- 24-28 October, **14th Meeting of the European Tumor Virus Group**, Bulgaria (Dr T.G. Todorov, Bulgarian Academy of Sciences, Inst. of General and Comparative Pathology, Acad. G. Bonchev str. Blok III, Sofia 1113, Bulgaria).
- 26-28 October, **Medical Imaging and Image Interpretation**, Berlin (Dr M.H. Loew, Dept of Electrical Engineering and Computer Science, George Washington University, Washington DC 20052, USA).
- 26-28 October, **Polynuclear Aromatic Hydrocarbons**, Columbus (Dr M. Cooke, Battelle's Columbus Laboratories, 505 King Ave, Columbus, Ohio 43201, USA).
- 29-31 October, **3rd General Meeting of the American Pain Society**, Miami (K.L. Casey, Chief Neurology Service, VA Medical Center, 2215 Fuller Rd, Ann Arbor, Michigan 48105, USA).
- 31 October-2 November, **The Society for Environmental Geochemistry and Health, 1st Annual Scientific Meeting**, North Carolina (C. Harrington, Dept of Surgery, School of Medicine, East Carolina University, Greenville, North Carolina 27834, USA).
- 1-5 November, **Effects of Ultraviolet Radiation on Plants**, Delhi (Prof. L.O. Bjorn, Dept of Plant Physiology, Box 7007, S-220 07 Lund, Sweden).
- 7-10 November, **Woodlands Conference on Sustainable Societies**, Texas (The Woodlands Conference, PO Box 9663, Arlington, Virginia 22209, USA).
- 8-10 November, **Applications of Accelerators in Research and Industry**, Texas (J.L. Duggan, Dept of Physics, PO Box 5368, North Texas State University, Denton, Texas 76203, USA).
- 7-10 November, **1st International Workshop on Human Leucocyte Differentiation Antigens**, Paris (Dr A. Bernard, Hôpital Saint-Louis, 2 Place du Docteur Fournier, 75475 Paris, Cedex 10, France).
- 16-19 November, **Applications of Biological Markers to Carcinogen Testing**, Bethesda (The Council for Research Planning in Biological Sciences, Inc. c/o Associated Universities, Inc. 1717 Massachusetts, NW 603, Washington DC 20036-2077, USA).